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WHAT IS LIPEMIC NEPHROSIS?*

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In this paper I shall discuss what is known as chronic genuine nephrosis or chronic lipemic nephrosis, wholly omitting such subjects as amyloid nephrosis, necrotizing nephrosis, febrile albuminuria, sublimate nephrosis, and so forth. It is chronic lipemic nephrosis, and not the other types, which has caused a great deal of discussion and research in the past 20 years and which has caused every internist a great deal of intellectual difficulty.

In 1914 Volhard and Fahr,[12] in their monograph on Bright's disease, set apart for the first time the entity which they called "chronic genuine nephrosis." They sharply defined, both clinically and anatomically, this supposedly distinct nephropathy. Since that time, many papers have been written about chronic genuine nephrosis, or as it is now more commonly known in the United States, chronic lipemic nephrosis. In my opinion, the general practitioner has been caused an unnecessary amount of difficulty because of this new name and also because of the introduction of certain conceptions that had previously not been considered in discussing kidney disease. I shall try to clear up this subject in a very simple way. At the outset, I want to state that pure forms of chronic nephrosis are really very rare. I have been looking for this condition since 1916 and have seen only 10 cases among the large number of nephropathies seen by me during this period. Volhard, who has probably

* Lecture delivered at Oklahoma City Clinical Association, 1933, and before the Lackawanna County Medical Society, 1935.

the largest material in kidney disease in the world at his command, speaks of its rarity. The pediatricians apparently see relatively more of this disease than do the internists. On the other hand, many of the cases described as chronic lipemic or chronic genuine nephrosis are, in fact, not chronic genuine nephrosis in the strict sense of the term, but are actually cases of glomerulonephritis which have in addition to the symptoms and laboratory findings characteristic of glomerulonephritis many of the characteristics of a lipoid nephrosis, the so-called subacute or subchronic glomerulonephritis with "*nephrotischem Einschlag.*"

At this point it may well be asked, what, then, is chronic lipemic nephrosis in the strict sense of the term? From the standpoint of symptomatology, it is a condition in which a most severe hydrops develops, as a rule insidiously. There is often a tremendous anasarca which, when a trochar is inserted into the lower extremity, results in the draining off of quarts of edema fluid, containing the water and salts of the blood plasma but none or extremely little of the albumin of the plasma. In other words, this edema fluid is a nearly pure transudate or ultrafiltrate.* There is usually a marked ascites and usually also hydrothorax on one or both sides. At autopsy, in cutting through the muscle and the connective tissue, one can sometimes see edema fluid oozing out from the interstices of the connective tissue. In addition, the patient usually has an anorexia which may be extremely severe, so that there is a marked reduction in the intake of food. In my estimation, some of these patients actually die of inanition. The patients are pale and weak, though not a few can carry on in their work or profession for some time, especially if most of the edema is removed by therapeutic measures. The most common cause of death is usually stated to be a pneumococcus peritonitis. Other causes of death are streptococcus peritonitis, pneumonia, and inanition. One of my 10 cases of pure nephrosis died in uremia. This important case will be described later in this paper.

I want to emphasize that according to the strict definition of true chronic nephrosis, the blood pressure is always normal and must be normal. A little farther on in this paper I am going to discuss 2 of my cases which were seemingly exceptions to this rule. One was an undoubted pure case, substantiated by the very careful autopsy studies of Dr. E. T. Bell, Professor of Pathology at the University of Minnesota. The other, on careful microscopic examination, showed minimal endothelial cell proliferation in some of the glomeruli, so that it was not 100% pure. In both cases high blood pressure developed before death. The study of these two kidneys by Dr. Bell together with the experimental studies of Bell,[3] Goldblatt,[8] Collins,[4] and Page[11] has thrown a most interesting light upon the mechanism of hypertension in kidney disease, and demonstrates

* This fluid contains from 0 to 0.15% of protein, averaging about 0.1%.

why the blood pressure is ordinarily not elevated in pure nephrosis. These cases will be described later in this paper.

The patient with chronic nephrosis has a severe obliguria, passing from 200 to 600 cc. of fluid during the 24-hour period. A specific gravity of from 1.025 to 1.050 is nearly always found, unless a diuresis has been induced by some method. There is a heavy flocculation of albumin, usually termed 4+, there being from 1 to 5% of albumin content in the urine and the daily output ranging from 10 to 30 grams or even more in a day. There are hyaline and granular casts in abundance. Sometimes the casts are studded with little highly refractile globules which, under the Nicol prisms, are seen to be doubly refractile. These small highly refractile globules may also be seen floating in the urine. They are cholesterol droplets. In a true case of genuine nephrosis, there are no red blood cells in the urine.* There are, on the other hand, always a few white cells. The urine occasionally shows traces of sugar and even moderate quantities of sugar at times, especially after a diet containing considerable carbohydrate. It has been found that this is a true renal glycosuria probably due to the fact that the reabsorption of sugar from the glomerular filtrate in the anatomically altered convoluted tubules of the kidney is impaired. If gum acacia or Congo red are introduced intravenously, then these substances appear in large quantities in the urine very soon. These two colloids are not found in the urine from normal kidneys. The Congo red and gum acacia particles leak through the glomerular ultrafilter and appear in the urine exactly in the same manner as the serum albumin particles of the plasma do.

Physicians of the older generation will say I am describing what they were brought up to call chronic parenchymatous nephritis or chronic tubular nephritis. Let me state at once that they are right, because what was formerly called chronic parenchymatous nephritis or chronic tubular nephritis is today divided into chronic genuine or lipemic nephrosis and subchronic glomerulonephritis with a nephrotic tendency (nephrotischem Einschlag) by those who follow the Volhard and Fahr classification.

What does the blood show? It shows that the serum albumin is reduced to extremely low values, around 1 to 3% instead of the normal 4 or 5%. The globulin remains at the normal value or seems even to increase at times. Fibrinogen seems always to be somewhat increased. Because of the lowered serum albumin content of the blood, the so-called colloid osmotic pressure is reduced to one-half or even less.

There is an increased neutral fat content of the blood and the values for cholesterol are doubled or tripled. On viewing the serum,

* One or two red blood cells per medium power field are occasionally seen in the urine of normal persons if a careful search is made. Not more than this many are seen in nephrosis.

one frequently notes that it is milky or creamy because of the large number of lipoid particles it contains. Hence the name lipemic nephrosis. There is usually some slight anemia or even a moderate anemia. Our experience has shown that careful determinations of the blood plasma volume usually show it to be somewhat, or even considerably, reduced. In other words, just the opposite of a plethora or hydremia is present. There is no increase in the metabolites of the blood, such as the non-protein nitrogen, the urea, the creatinine, the indican, and so forth.

Let us now inquire as to the kidney function. The water output is remarkably reduced and with this, the output of salt. But, as I will show a little later, this is not due to a diminution in kidney function, but is a result of the loss of serum albumin and the consequent reduction in the colloid osmotic pressure. In consequence of the lowered colloid osmotic pressure, water and salt filter off from the plasma in the capillaries to form edema. The urine output is reduced exactly by the amount of water and salt retained as edema. In my experience, the output of phenolsulphonephthalein dye is normal, or even increased when the test has been made by intravenous injection of the dye and when the urine has been obtained by catheterization and irrigation of the bladder to obtain all the urine in the bladder. The concentration test is normal. There is no tendency whatsoever to true uremia, nor to pseudouremia or eclamptic uremia. At times, there seems to be a slight haziness about the nerve head which suggests the possibility of some edema; otherwise the eyegrounds are normal.

The basal metabolism is nearly always lowered to values of from -10 to -30%, which has suggested to certain physicians that nephrosis may be a disease of metabolism. In only one case have I ever found outright symptoms of myxedema in nephrosis, and in this case the nephrosis cleared up with the cure of the myxedema by thyroid extract. When the thyroid extract was no longer taken, both the symptoms of myxedema and of nephrosis reappeared in the patient.

Pathology. The kidney at autopsy is seen to be slightly or much enlarged, to be pale grayish-yellow, and to look fatty. On microscopic examination, the convoluted tubules show swelling of the cells and infiltration with hyaline droplets or infiltration with fat and lipoid bodies which are doubly refractile. Using the ordinary hemotoxylin-eosin stain, only slight changes or none at all are seen in the glomeruli. The earliest accounts of histologic examination stated that the glomeruli were altogether normal. On the other hand, Dr. E. T. Bell,[2] of the department of pathology at the University of Minnesota, using the azocarmine dye, has shown that the glomerular basement membrane shows distinct changes in many cases. These are a thickening of this membrane and apparently some fraying out of the membrane. In other words, the filtering

membrane in many cases of this disease seems to have undergone some anatomic change. It can no longer be said that the glomeruli are normal, because as this disease progresses, this basement membrane gets thicker and thicker, at times to such a degree that the circulation in the glomerular loops may be throttled. In consequence, high blood pressure may develop and renal insufficiency and uremia may result from the impaired flow of blood through the glomerulus and the marked decrease in the area of filtering surface brought about by this thickening of the basement membrane. This happened in two of our most interesting cases, on which we have complete autopsy examinations. In my opinion, this thickening of the basement membrane, but more especially the changes in its function as an ultrafilter, are the crux of the whole situation in chronic lipemic or chronic genuine nephrosis.

As to the etiology of the disease, frequently it is altogether unknown. I have seen one case develop after a sore throat, much as acute glomerulonephritis does, but without the hypertension, hematuria and renal insufficiency characteristic of true glomerulonephritis. I have seen one case in a physician, apparently after a severe streptococcus infection of the finger. The finger finally healed, but during the infection, what was called nephritis developed. When I saw the patient about 2 years after the original infection, he had a typical case of true chronic lipemic nephrosis. In children it is often associated with a purulent sinusitis from which *Staph. albus* can be cultured. I have seen one case associated with a true myxedema which cleared up completely after curing the myxedema on thyroid administration. Occasionally syphilis will cause a chronic nephrosis. Many of the cases develop insidiously without any clear-cut evidence for an etiologic agent.

Now that I have given you this picture of chronic lipoid nephrosis, let us see what he can make out of it through our knowledge of modern physiology and research. To my mind, all the symptoms of the disease can be easily explained on the well-founded assumption that the ultrafilter of the glomerulus, which has been shown in most cases to be altered morphologically by the newer staining methods, has become permeable to serum albumin and other colloids of small size. Therefore the serum albumin in the blood filters off into the urine day by day. The content of serum albumin in the blood is hereby reduced to such values that the colloid osmotic pressure of the blood is lowered to about one-half.

At this point let me say just a word or two about this osmotic pressure of the colloids of the blood. In my estimation, the only known function of the serum albumin in the blood plasma is to produce a colloid osmotic pressure within the capillaries of the body. Because the serum albumin can not pass through the capillary wall as the salts and water can, the colloid osmotic pressure is effective only inside the capillaries and therefore tends to hold water within

the capillaries against the hydrostatic pressure in these capillaries which tends to filter off the water and salts of the plasma into the tissue as an ultrafiltrate. If we had not this colloid osmotic pressure, all the water and salts of our blood would, within a very few hours, leave the blood-vessels as a transudate and our blood would dry up to corpuscles.

Figure 1 is a diagram which illustrated what happens in the normal capillaries of the body when blood of normal colloid osmotic pressure flows through them. For the hydrostatic pressures at the arterial

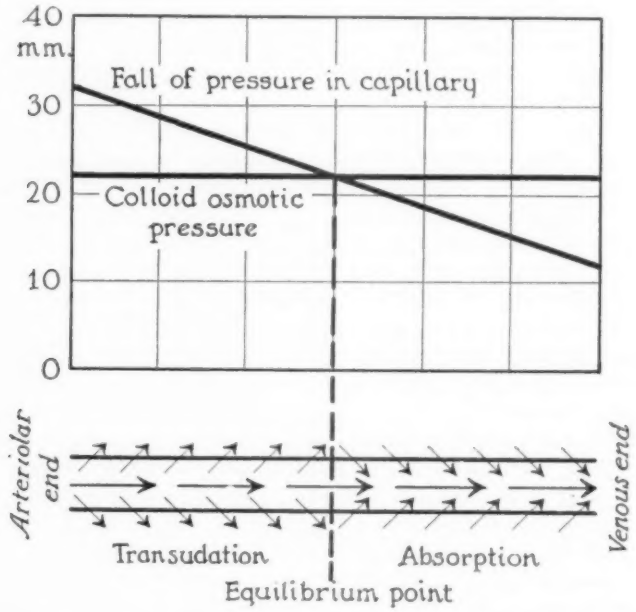

FIG. 1a.—Diagram of normal fall in pressure along human capillaries from the arterial end to the venous end, together with a normal colloid osmotic pressure. Plasma fluid is filtered out from the arterial half of the tube and reabsorbed in the venous half.

and venous ends of the capillaries I have used the averages obtained by Landis[9] from direct measurements on the capillaries of normal men. The normal colloid osmotic pressure I have taken as being 22 mm. Hg.[6] At the arterial half of the capillary there is ultrafiltration of water and salts from the capillaries into the surrounding tissue space, because the blood pressure or hydrostatic pressure is greater than the colloid osmotic pressure of the plasma proteins, and in consequence fluid and salts must pass out of the capillary as an ultrafiltrate or transudate. From the middle of the capillary on to the venous end the capillary blood pressure is less than 22 mm. Hg, and therefore water and salt must reënter the capillary, be-

cause the colloid osmotic pressure is higher than the hydrostatic pressure. The net result is: no loss of fluid from the blood plasma with normal colloid osmotic pressure flowing through this normal capillary. In Figure 2 is shown what must happen in a capillary if the blood pressure remains normal, but if the colloid osmotic pressure of the plasma is reduced to 12 mm. Hg. In this latter case the blood pressure is higher than the colloid osmotic pressure from the arterial to the venous end and filtration of water and salts will take place all along the capillary and there will be no reabsorption

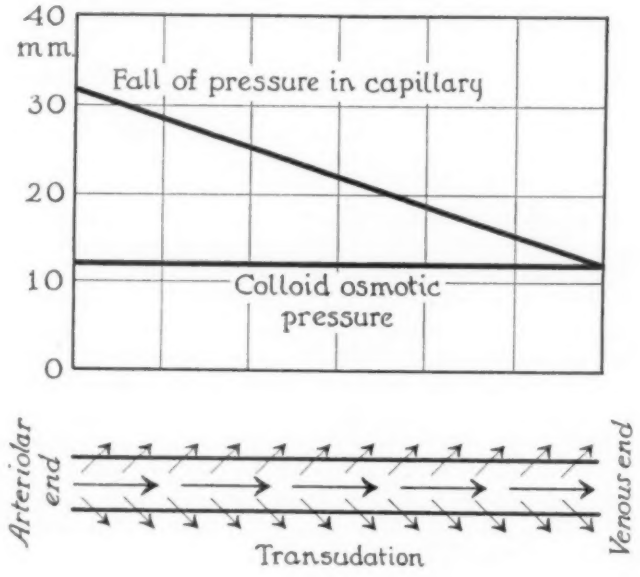

FIG. 1*b*.—Diagram of normal fall in pressure along the capillary, with low colloid osmotic pressure of 12 mm. Hg. Plasma fluids must be filtered out along the whole course of the capillary from arterial end to venous end, and this fluid, collecting in the interstices of the white fibrous connective tissue, becomes edema.

in this capillary. The excess fluid may be partly taken care of by the flow of lymph away from the area, but some fluid will remain as edema and less fluid will get to the kidneys for filtration. The result will be edema and oliguria, both due to reduction in colloid osmotic pressure alone.

Therefore when the colloid osmotic pressure in nephrosis is reduced to one-half or near it, much of the ingested water and salt is filtered off into the skin and other tissues. Under these circumstances only a small portion of the ingested water and salt is available for filtration in the glomeruli of the kidneys and the urine output is reduced to a small fraction of the ingested water and salt. The water and salt filtered off in the capillaries accumulates in the

subcutaneous and other connective tissue reservoirs and we begin to have an edema. This has been proved by research work done on animals by Leiter,[10] Barker,[1] Fahr and Kerkhof.[5] If we take away from our experimental animals by plasmapheresis* so much of the serum albumin and globulin that the colloid osmotic pressure is reduced to one-half, then our animals develop the same kind of hydrops as do our patients with chronic nephrosis. A diuresis follows at once and a rapid removal of the edema fluid takes place if gum acacia, an indifferent colloid, is injected into the veins of our patients or into the veins of our experimental dogs suffering from this type of edema. The gum acacia serves only to raise the colloid osmotic pressure of the blood plasma. Edema fluid in large quantities is then drawn into the capillaries and circulates with the blood plasma to the kidneys where it is rapidly removed as urine. Not infrequently one can see the distended veins swollen with the increased blood volume due to the absorption of the edema fluid. Blood volume determinations done after the injection of the gum acacia prove that the blood plasma volume is increased and that actually a plethora or hydremia has been produced.

The experimentally produced hydrops has been proved by our researches to be a true transudate, containing very little of the protein of the blood, but containing salts and water. The edema fluid in our experimental animals is the same as in nephrosis. Moreover, in these animals when we begin to remove the serum albumin of the blood and to lower its protein content, the lipoid and fat content of the blood immediately rise somewhat. And just as the plasma volume is reduced in chronic lipemic nephrosis, so also is the plasma volume reduced in our dogs in these experiments, despite the fact that there has been no loss of corpuscles. When gum acacia is injected, the plasma volume increases to the normal or higher values.

Very much has been made of the low basal metabolic rate by many authors in discussing the etiology of the condition. In my estimation, there are three factors producing this low basal rate. First, in calculating the basal metabolism from the height-weight formula, we usually do not subtract the weight of the accumulated water. The inclusion of this extra weight of water in the calculation tends to lower the determined basal metabolism as over against the calculated one by about 5 to 10%. Also I have determined on some of my cases that these patients eat much less than their basal requirements and therefore are in a state of chronic starvation. As is well known, chronic starvation reduces the basal metabolism.

* By plasmapheresis we mean the abstraction of serum protein from the blood plasma. The dogs are repeatedly bled from the right heart or jugular veins. The blood plasma is pipetted off the centrifugalized blood corpuscles. The blood corpuscles plus Ringer's solution is reinjected. If done carefully there is no reduction in the number of red cells in the blood but a very marked reduction in the plasm proteins. We have produced a severe edema within 24 hours in our dogs by this method.

A diet of 800 calories per day sometimes lowers the basal metabolic rate as much as 10%. I have had one patient with a subchronic glomerulonephritis with a strong nephrotic tendency who lived on an intake of about 500 calories per day for some months and finally died of inanition. His basal rate was around −20%. Moreover, I am inclined to believe that the thyroid hormone circulating in the blood may be filtered off to a considerable amount in the urine just as are serum albumin, gum acacia, Congo red, and other colloid particles of small size. I have given enormous quantities of thyroid extract, 10 to 15 grains, daily to these patients without raising the basal metabolism more than a few degrees and without causing symptoms of hyperthyroidism. These same quantities given to normal persons or even to patients with true myxedema would probably raise the basal rate far above the normal and would cause symptoms of tachycardia, nervousness, palpitation and weakness. In fact, I have seen what was apparently exophthalmos develop in 2 patients with myxedema who were given doses of thyroid extract comparable to doses that are frequently given in the treatment of chronic nephrosis without the production of symptoms of hyperthyroidism.

There may very well be a moderate degree of hypothyroidism present in chronic nephrosis, but of a degree insufficient to produce outspoken symptoms of myxedema. Barker[1] has shown on animals that a chronic lowering of serum protein by plasmapheresis leads to a lowered basal rate. It is possible that Barker's dogs did not eat as well as normal dogs and in removing the serum proteins by plasmapheresis circulating thyroid hormone was removed at the same time, both tending to lower the basal rate. The above mentioned factors, I think, will explain the lowered basal rate in most cases. Certainly very few of the cases have the mental characteristics of myxedema in any severe degree, and there does not seem to be either the skin change, the loss of hair, or the intolerance to cold so characteristic of myxedema.

It is a well known fact that hypercholesteremia follows hypothyroidism and lowered basal rate. I believe that some of the hypercholesteremia of chronic nephrosis is associated with the hypothyroidism and lowered basal rate. There is also experimental evidence found in plasmapheresis experiments that an increased cholesterol and neutral fat content of the blood plasma follows depletion of the proteins of the blood plasma.[7] In some of our own experiments on plasma protein depletion in dogs, we saw increases in the plasma lipoids appear. Therefore it does not seem necessary to call in other mechanisms to explain the lipemia of chronic nephrosis.

In our dogs we find exactly what we find in these patients, except that we remove the serum albumin from the blood mechanically, whereas in chronic nephrosis it is removed by a pathologic permeability of the glomerular membrane which is normally impermeable

to serum albumin and globulin. I think it can be said that, although we have not produced the characteristic picture in the kidney of chronic genuine nephrosis, we have produced in our animals the symptomatology of chronic lipemic nephrosis and have learned something of the exact mechanism of the production of these symptoms. The pathologic changes in the kidney of nephrosis, our knowledge of kidney function, and the data obtained from our dogs in which the plasma proteins have been depleted compel us to believe that chronic genuine or lipemic nephrosis is a disease of the glomerulus of the kidney, of such a nature that where as previ-

FIG. 2a.—Photomicrograph of a glomerulus in a case of pure nephrosis which died in uremia. The basement membrane thickening and the intense narrowing of the lumen of many of the glomerular capillaries can be seen. Many glomeruli are completely closed and hyalinized. Azo carmine stain.

ously it held back serum albumin and allowed the plasma to be filtered off as an ultrafiltrate, now in this disease, it has become permeable also to serum albumin and as the plasma water and salt filters off in the glomerulus, part of the serum albumin goes with it and is found in the urine. The reduction of the content of the serum albumin in the blood lowers the colloid osmotic pressure and this leads to an increased formation of transudate in all the capillary areas of the body. This transudate forms faster than the lymph flow can remove it and edema develops.

Moreover, our experiments on animals and on patients have proved that the retention of salt is due to the lowering of the colloid

osmotic pressure and the accumulation of edema, rather than that the salt causes the edema in itself. In our animals we have lowered the serum albumin content to one-half or less and then we have replaced a large part of the serum protein of the blood by gum acacia, keeping the colloid osmotic pressure nearly normal by means of the gum acacia. Under these circumstances, water output was normal, no edema formed and no salt retained. We have replaced the serum albumin in our patients by another colloid, gum acacia, and have caused the absorption of the edema in this disease and have produced a very good diuresis of water and sometimes as much as a tenfold increase in the daily output of salt. Moreover, in our animals the neutral fat increase in the blood is shown to be partly due to the reduction of the serum protein content in the blood.

The degenerative changes in the convoluted tubules are as yet not well explained. For myself, I believe that the infiltration with fat and lipoid is due to the fact that there is an increased content of the fat and lipoid in the blood and in consequence the glomerular filtrate which passes down the kidney tubules probably has a high fat and cholesterol content. We know there is always some fat and lipoid in the urine. It is not at all improbable from our knowledge of kidney function that the cells of the tubules simply infiltrate with this lipoid and fat and possibly also with albumin. We have not yet gone far enough in our experiments to prove this point, but Barker[1] has described hyaline droplets and fatty infiltration in the kidneys of his dogs with reduced plasma protein content and high lipoid content of the plasma.

Certainly from the present state of our knowledge of the physiology of these kidneys, there is no marked change in the function of the tubules, excepting occasionally some sugar in the urine, which is the only indication that I have ever found that the tubular function is damaged in this disease. It is now well known that in the tubules, especially in the convoluted tubules, the salt and sugar filtered off in the glomerulus is reabsorbed and there is nothing as yet to show that this salt is not reabsorbed in chronic genuine nephrosis. In fact, there is an increased retention of salt in these cases. This retention, as our animal experiments show, is due to the retention of edema through the lowering of colloid osmotic pressure and not to tubular degeneration in the kidney (Ref. 1, 3d paper).

Before I proceed further with this discussion, I want to describe 2 of our most interesting cases of this disease.* One of these was a colleague who had chronic genuine nephrosis in the ordinary form for 5 years. He was investigated at the Rockefeller Institute, was studied by Dr. Berglund of the University of Minnesota, by the late Dr. John Phillips of the Cleveland Clinic, and by myself for a long time. For the first 5 years of his illness his symptoms were

* These cases are to be reviewed in a paper soon to be published by Dr. E. T. Bell and the author.

edema and a moderately severe albuminuria. There was never any hypertension nor any signs of renal insufficiency prior to 1931. There was no hematuria. Everyone concurred that he was the purest type of chronic genuine or lipemic nephrosis until in February, 1931. About this time it was noted that his blood pressure had risen above the normal. During the kidney symposium held at the University of Minnesota in July, 1931, he asked for consultation with Professor Volhard. It was found that his blood pressure was rising and soon after this reached a systolic of 250. His glomerular function, as shown by the kidney function tests, was becoming impaired and Professor Volhard said "This is not chronic genuine nephrosis. He has high blood pressure; he already has signs of renal insufficiency. This is a case of subchronic glomerulonephritis." I never changed my opinion, even then, because red blood cells never came down in his urine until his heart began to fail somewhat later. It is a fact that the blood pressure went up and finally reached extremely high values. It is true that renal insufficiency increased and that he died with a combination of heart failure and true uremia in 1932. Not until the autopsy was the riddle solved and the differences of opinion explained. At that time, we found that the glomerular basement membrane had increased in thickness until it throttled off the circulation through the glomerular capillary loops* (Fig. 2*a*). Many glomeruli were found to be hyalinized and the corresponding tubules were found to be atrophic. Some of the glomerulotubular units had disappeared and were found replaced by scar tissue. There was no increase in the endothelial or epithelial cells.

We now know, through animal experimentation done by Bell[3] and Pedersen, Goldblatt,[8] Collins,[4] and Page[11] that with this throttling of the circulation, the blood pressure always goes up. It can be seen very easily from the degree of narrowing of the lumen of the capillaries in this case that the flow of blood through his glomeruli must have been reduced very considerably by the narrowing of the capillary lumen.† Moreover, it can be seen that the filtering surface has been reduced very much because of the narrowing of the lumen of the capillaries.‡ The rate of filtration in the glomeruli of this patient must have been reduced to much less than one-fourth the normal. His glomerular filtering function necessarily had to fail because of this throttling process, and metabolites were forced to accumulate because of the impairment of this most important renal function.

* For a description of the kidney in this case, see Bell, E. T., loc. cit.

† If the blood pressure at the arterial and venous ends of a capillary is kept constant and the diameter of the lumen of the tubing reduced to one-half, then according to Poiseuilles' law the flow of blood through the capillary is reduced to one-sixteenth of its previous value!

‡ The diameter of the inside of the glomerular capillaries determines exactly the area of the filtering surface in the glomerulus, provided the number and length of these capillaries remains constant. If the diameter is one-half the original capillary diameter and everything else remains constant, the rate of filtration becomes one-half.

He died of uremia just as we would expect him to die, from examination of his kidneys. But in his kidneys, there was not the slightest sign of that type of lesion which is always associated with glomerulonephritis. In other words, there was no endothelial cell proliferation anywhere, no intracapillary fibrils and no epithelial cell proliferation. In glomerulonephritis it is the endothelial cell proliferation, the intracapillary fibrils and the epithelial cell proliferation which cause the throttling of the circulation through the glomerulotubular units and which together with the hyalinization

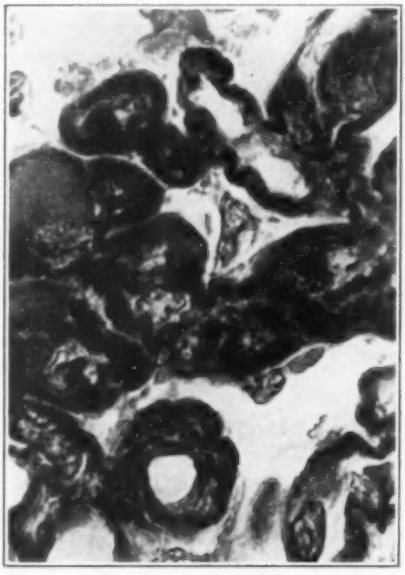

FIG. 2*b*.—Higher magnification of a small area of the same glomerulus. The great thickening of the basement membrane is well shown. The capillaries in the upper left hand corner are practically completely closed by basement membrane thickening where this section was made. Capillary lumens in the lower left hand corner are open and only moderately narrowed. No increase in endothelial cells or epithelial cells. These photomicrographs were obtained through the courtesy of Dr. E. T. Bell, Professor of Pathology, University of Minnesota.

of glomeruli and tubular atrophy bring about renal insufficiency and uremia. In this case of nephrosis it was the increasing thickening of the basement membrane that brought about the reduced blood flow, ischemia and renal insufficiency.

The other case from the Minneapolis General Hospital service was practically the same in every respect excepting that there always was some hypertension and there were always a few red cells present in the urine. The hydrops in this case was exceptional. The patient was completely incapacitated by an immense anasarca and ascites together with hydrothorax. Histologic examination of

the kidneys showed a small amount of endothelial cell proliferation on careful search. In other words, this case was not quite 100% pure. Thickening of the basement membrane about the glomerular capillary tufts was the outstanding pathologic change in these kidneys. In this case also some of the glomeruli had become completely hyalinized, because blood flow was completely stopped by the thickening of the basement membrane of the glomerular capillaries. The tubules corresponding to the glomeruli with throttled circulation had atrophied. This atrophy as well as the absorption of hyalinized units led to a decrease in size and some pitting of the surface of these kidneys. These cases furnish, in my mind, the best proof that the real and essential pathologic process in chronic lipemic or genuine nephrosis is the change in the basement membrane, its thickening on the one hand, and its increased permeability for small colloid particles on the other. When this thickening increases to the point where the glomerular circulation is throttled, then blood pressure must rise. With the decreased flow of blood through the glomeruli and the decreased filtering surface produced by the marked membrane thickening about the glomerular tufts, renal insufficiency must ensue, and finally uremia must develop and the patient must die in true uremia.

If chronic genuine nephrosis were a distinct pathologic and clinical entity, we should not expect to find its pathologic and clinical characteristics frequently associated with the pathologic and clinical findings of glomerulonephritis. But as an actual matter of fact, cases of pure nephrosis are very rare, whereas cases of glomerulonephritis accompanied by the characteristic symptoms of nephrosis, heavy albuminuria, low serum albumin content of the plasma, marked hydrops, lipemia, and lowered basal rate are really very common. In these cases of subacute and subchronic glomerulonephritis with nephrotic tendency one finds in addition the characteristic symptoms of glomerulonephritis, namely hypertension, hematuria and renal insufficiency. On examining these kidneys one finds not only the endothelial cell and epithelial cell proliferation characteristic of glomerulonephritis but often also the basement membrane changes characteristic of chronic nephrosis. Neither clinically or pathologically is it frequently possible to separate the symptoms and signs characteristic of nephrosis and glomerulonephritis. They are not distinct entities excepting in rare cases but are usually found together. Chronic genuine nephrosis or lipemic nephrosis is only a term that attempts to differentiate as a distinct disease part of the usual picture of subacute and subchronic glomerulonephritis. Therefore it is a part of the picture of glomerulonephritis which occasionally becomes so prominent in the picture that when associated with an absence of the characteristic hypertension and hematuria it seems to be a distinct clinical and pathologic entity until critically examined in the light of all the

facts of symptomatology and pathology. The symptoms and signs of chronic genuine or lipemic nephrosis are only part of the picture of glomerulonephritis. We should learn to think of the symptoms of albuminuria, lowered plasma proteins and hydrops as associated with anatomic and physiologic changes in the ultrafiltration membranes of the glomerulus of the kidney and the hematuria hypertension and renal insufficiency with the obstruction of the glomerular capillaries by endothelial cell proliferation and other obstructive and destructive processes in the glomerulus and with the consequent throttling of the glomerular circulation. We thus approach one of the ideals of medical diagnosis; namely, the reference of symptoms to altered physiology and the correlation of this altered physiology with the findings of pathologic anatomy.

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ABSENCE OF PEPTIC ULCER IN PERNICIOUS ANEMIA.

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The theories of the etiology of chronic peptic ulcer have been reviewed by numerous writers.[2] Since hyperchlorhydria has been incriminated as a possible factor in the pathogenesis of chronic peptic ulcer, a determination of the frequency of chronic peptic ulcer in individuals with a known achlorhydria has been undertaken. A review was made of the charts of all patients with pernicious anemia admitted to 9 hospitals* during the period extending from 1921 to 1936. This disease was chosen because of the known absence of free hydrochloric acid in the stomach.[5]

The clinical records of 840 patients with pernicious anemia were examined. Of these, 616 had at least one analysis of gastric content while in the hospital. None of these showed the presence of free

* Permission to use the records of Lakeside Hospital, City Hospital and Mount Sinai Hospital, Cleveland, Beth Israel, Israel Zion, Beth Moses and Mount Sinai Hospitals, New York, and the Cincinnati General Hospital, is gratefully acknowledged.

hydrochloric acid. Sturgis[5] has shown that achlorhydria is constant in pernicious anemia. Thus it is fair to assume that all the remaining 224 patients or at least a high percentage of them, had achlorhydria.

The following tables are inserted to show that the ages of the patients with pernicious anemia and those with chronic peptic ulcer coincide sufficiently to justify a comparison of the two groups. Table 1 gives the number and sex of 620 of the patients with pernicious anemia in the different age groups. Circumstances made it impossible to secure the age and sex of the other 220 cases.

TABLE 1.—AGE AND SEX DISTRIBUTION OF PATIENTS WITH PERNICIOUS ANEMIA.

	Years.									
	1–10.	11–20.	21–30.	31–40.	41–50.	51–60.	61–70.	71–80.	81–90.	Total.
Number of patients	2	2	16	68	138	215	124	54	1	620
Females	2	1	9	40	81	99	62	27	0	321
Males	0	1	7	28	57	116	62	27	1	299

Table 2[3] gives the number and age of a series of patients with chronic peptic ulcer who were studied clinically.

TABLE 2.—AGE DISTRIBUTION OF PATIENTS WITH CHRONIC PEPTIC ULCER.

	Years.							
	0–20.	20–30.	30–40.	40–50.	50–60.	60–70.	70–.	Total.
Number of patients	14	167	261	224	130	66	12	921

Females, 672; males, 249.

Examination of these tables shows that the highest incidence of pernicious anemia is in the sixth decade, whereas, that of peptic ulcer is in the fourth decade. The distributions differ in that in pernicious anemia there is a sharp peak in the sixth decade, whereas, the curve of peptic ulcer is flatter and still has a high incidence in the fifth decade; 90.8% of the cases of ulcer and 90.1% of the cases of pernicious anemia occur by the end of the sixth decade. Thus it is apparent that in spite of the difference in the peaks of the age incidence, there is sufficient overlap to justify the consideration of peptic ulcer as a disease that could have occurred in the age group of many of the patients with pernicious anemia.

In none of the 840 patients with pernicious anemia was a diagnosis of chronic peptic ulcer made during the time that they were in the hospitals, and in only 2 was there any history at any time of ulcerative lesion of the stomach.

Clinical Notes. One patient, a white male, aged 28, was operated upon for peptic ulcer 10 years before admission to Lakeside Hospital with pernicious anemia. A posterior gastro-enterostomy had been performed and after the operation he had no complaints referable to peptic ulcer. Three

roentgenographic examinations of the gastro-intestinal tract were performed while he was in the hospital for pernicious anemia and a diagnosis of persistent peptic ulcer could not be made upon the basis of clinical or roentgenographic examination.

Another patient, a white male, aged 76, had a bleeding peptic ulcer 2 years before admission to Lakeside Hospital with pernicious anemia. The diagnosis of pernicious anemia was established 1 year before admission to the hospital and 1 year after his peptic ulcer developed. From the time the signs and symptoms of pernicious anemia developed he had no signs or symptoms of peptic ulcer. He was given hydrochloric acid while in the hospital but developed no gastric discomfort. Roentgenograms of the stomach favored the diagnosis of carcinoma rather than gastric ulcer.

Of the remaining 838 patients, 129 had roentgenographic studies of the gastro-intestinal tract. Forty autopsies were performed; 3 on patients who had roentgenographic studies. Neither the roentgenographic studies nor the autopsies revealed the presence of a chronic peptic ulcer. The remaining 669 patients showed no signs or symptoms of existing peptic ulcer, nor gave a history of having had that lesion at any previous time.

Brown[1] gives the incidence of peptic ulcer in the people of North America as 1.3%; Stevens,[4] as 1.2%. Therefore, in this series there should be, on the basis of these figures, 11 to 17 patients with chronic peptic ulcer. Since none of the patients had peptic ulcer at the time of admission to the hospital with pernicious anemia, and since there is achlorhydria in all true cases of pernicious anemia,[5] the results of this study indicate that hydrochloric acid in the stomach may be of significance in the pathogenesis and persistence of peptic ulcer. How important this is, cannot be stated on the basis of this study, especially when consideration is given to the frequent absence of pepsin and the antianemic factor from the gastric secretions of patients with pernicious anemia. If it be found, as a result of other surveys of this kind, that chronic peptic ulcer rarely or never develops in a patient with pernicious anemia, it may be safe to infer that at least normal acidity, or perhaps hyperacidity, is one of the conditions necessary for the development of chronic peptic ulcer. As a matter of fact, in another type of anemia, chlorosis, in which there is hyperchlorhydria, the incidence of peptic ulcer is said to be high, but indubitable proof of this on the basis of autopsy findings is wanting. The stomach in pernicious anemia usually shows either mucosal atrophy or chronic atrophic gastritis. It would be mere speculation to attempt to correlate this morphologic change with the absence of peptic ulcer. It is of passing interest, however, that many instances of chronic peptic ulcer are associated with chronic hypertrophic gastritis.

Summary. The records of 840 patients with a well-supported diagnosis of pernicious anemia have been examined. Many of these had proven achlorhydria and it is fair to assume that practically all had this functional disturbance. It is of interest and probably significant that none of these patients had peptic ulcer at the time they had pernicious anemia with its associated achlorhydria.

hydrochloric acid. Sturgis[6] has shown that achlorhydria is constant in pernicious anemia. Thus it is fair to assume that all the remaining 221 patients or at least a high percentage of them, had achlorhydria.

The following tables are inserted to show that the ages of the patients with pernicious anemia and those with chronic peptic ulcer coincide sufficiently to justify a comparison of the two groups. Table 1 gives the number and sex of 620 of the patients with pernicious anemia in the different age groups. Circumstances made it impossible to secure the age and sex of the other 220 cases.

TABLE 1.—AGE AND SEX DISTRIBUTION OF PATIENTS WITH PERNICIOUS ANEMIA.

	Cases									
	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	Total
Number of patients	2	2	16	68	138	213	124	54	1	620
Females	2	1	9	40	81	99	62	27	0	321
Males	0	1	7	28	57	114	62	27	1	299

Table 2[5] gives the number and age of a series of patients with chronic peptic ulcer who were studied clinically.

TABLE 2.—AGE DISTRIBUTION OF PATIENTS WITH CHRONIC PEPTIC ULCER.

	Cases									
	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	Total
Number of patients	14	167	361	224	109	66	21	3	0	965

Females, 672; males, 293.

Examination of these tables shows that the highest incidence of pernicious anemia is in the sixth decade, whereas, that of peptic ulcer is in the fourth decade. The distributions differ in that in pernicious anemia there is a sharp peak in the sixth decade, whereas the curve of peptic ulcer is flatter and still has a high incidence in the fifth decade; 50.8% of the cases of ulcer and 30.4% of the cases of pernicious anemia occur by the end of the sixth decade. Thus it is apparent that in spite of the difference in the peaks of the age incidence, there is sufficient overlap to justify the consideration of peptic ulcer as a disease that could have occurred in the age group of many of the patients with pernicious anemia.

In none of the 540 patients with pernicious anemia was a diagnosis of chronic peptic ulcer made during the time that they were in the hospitals, and in only 2 was there any history at any time of ulcerative lesion of the stomach.

Clinical Notes. One patient, a white male, aged 28, was operated upon for peptic ulcer 10 years before admission to Lakeside Hospital with pernicious anemia. A posterior gastroenterostomy had been performed and after the operation he had no complaints referable to peptic ulcer. The

roentgenographic examination of the gastrointestinal tract was performed while he was in the hospital for pernicious anemia and a diagnosis of pernicious anemia was established. He was given liver extract and roentgenographic examination.

Another patient, a white male, aged 76, had a bleeding peptic ulcer 2 years before admission to Colorado Hospital with pernicious anemia. The diagnosis of pernicious anemia was established 1 year before admission to the hospital and 1 year after he had peptic ulcer developed. From the time the signs and symptoms of pernicious anemia developed he had no signs or symptoms of peptic ulcer. He was given hydrochloric acid while in the hospital but developed no peptic dissemination. Roentgenograms of the stomach favored the diagnosis of carcinoma rather than gastric ulcer.

Of the remaining 828 patients, 120 had roentgenographic studies of the gastro-intestinal tract. Forty autopsies were performed on patients who had roentgenographic studies. Neither the roentgenographic studies nor the autopsies revealed the presence of a chronic peptic ulcer. The remaining 660 patients showed no signs or symptoms of existing peptic ulcer, nor gave a history of having had that lesion at any previous time.

Brown gives the incidence of peptic ulcer in the people of Natal, Africans as 0.2%, Slavonic, as 1.2%. Therefore in this series there should be, on the basis of these figures, 10 to 12 patients with chronic peptic ulcer. Since none of the patients had peptic ulcer at the time of admission to the hospital with pernicious anemia, and since there is achlorhydria in all true cases of pernicious anemia, the results of this study indicate that hydrochloric acid in the stomach may be of significance in the pathogenesis and persistence of peptic ulcer. How important this is, cannot be stated on the basis of this study, especially when consideration is given to the frequent absence of pepsin and the antianemic factor from the gastric secretions of patients with pernicious anemia. If it be found, as a result of other surveys of this kind, that chronic peptic ulcer rarely or never develops in a patient with pernicious anemia, it may be safe to infer that at least normal acidity, or perhaps hyperacidity, is one of the conditions necessary for the development of chronic peptic ulcer. As a matter of fact, in another type of anemia, chlorosis, in which there is hyperchlorhydria, the incidence of peptic ulcer is said to be high, but indubitable proof of this on the basis of autopsy findings is wanting. The stomach in pernicious anemia usually shows either mucosal atrophy or chronic atrophic gastritis. It would be mere speculation to attempt to correlate this morphologic change with the absence of peptic ulcer. It is of passing interest, however, that many instances of chronic peptic ulcer are associated with chronic hypertrophic gastritis.

Summary. The records of 840 patients with a well-supported diagnosis of pernicious anemia have been examined. Many of these had proven achlorhydria and it is fair to assume that practically all had this functional disturbance. It is of interest and probably significant that none of these patients had peptic ulcer at the time they had pernicious anemia with its associated achlorhydria.

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RADIATION AND CHOLECYSTECTOMY AS THERAPEUTIC PROCEDURES FOR TYPHOID CARRIERS.

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The chief problem in the treatment of typhoid carriers is the elimination of residual infection from the digestive tract. The intelligent application of therapeutic measures directed toward this end requires a knowledge of the location of the infection. Investigations have, of late, dealt particularly with this aspect of the problem and, chiefly through the use of duodenal drainage as a diagnostic procedure, the infection has usually been located within the biliary tract. That such biliary tract involvement is often limited to the gall bladder is indicated by the fact that cholecystectomy has frequently led to consistently negative feces cultures. Bigelow and Andersen[1] claim to have cured by cholecystectomy all of the 12 carriers whose duodenal fluid contained typhoid organisms, and Hanssen,[3] by so treating 5 carriers with infected bile, was similarly successful. Thus, the recovery of infected bile may reasonably be regarded as indication of involvement of the gall bladder and, together with Roentgen evidence of impaired function of that organ or of the presence of stones, warrants consideration of cholecystectomy.

Cholecystectomy, however, is often not feasible, either because of the age or the general condition of the patient or because of his unwillingness to submit to operation. In the treatment of such persons and of those who carry infection in the liver, in the intestine or in the urinary tract, an effective non-surgical procedure is needed. For many years various medical measures have been tried but without success.[4] The recent report of Gulbrandson[2] describing the effective use of radiotherapy was, therefore, received with great interest. Treating 12 carriers with small doses of Roentgen ray directed over the liver, he found 4 free from infection and the remainder with some decrease in the number of typhoid bacilli in

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the feces. In view of such encouraging results further trial of the method seemed desirable.

In the present investigation 22 carriers were studied, 12 of them later being treated by the method of Gulbrandson and 2 by cholecystectomy. In all but 1 who was a urinary carrier, cultures of the duodenal contents before treatment showed typhoid organisms, and gall bladder function was impaired as determined by Roentgen examination. Radiation was entirely ineffective in eradicating the infection. Cholecystectomy, on the other hand, was followed by relief from infection in each instance.

TABLE 1.—FACTS ELICITED FROM THE HISTORIES OF 22 TYPHOID CARRIERS.

Patient.	Age.	Sex.	History of typhoid fever.	Interval between infection and identification as carrier.	Length of time known to be carrier.	Cause of identification as carrier.	Number of cases of typhoid fever attributed to carrier.
1	54	M	Yes	None	1 yr.	Hospitalization during disease	0
2	34	M	0	...	3 yrs.	Case in house	1
3	59	F	0	...	2 "	Case in house	2
4	40	M	0	...	2 "	Case in house	1
5	77	F	Yes	28 yrs.	2 "	Case in house	1
6	75	F	2x	35 "	5 "	Case in house	1
7	65	F	0	...	5 "	Case in house	1
8	50	F	0	...	4 "	Case in house	1
9	58	M	Yes	None	11 "	Hospitalization during disease	0
10	37	F	Yes	7 yrs.	1 yr.	Case in house	2
11	62	F	0	...	3 yrs.	Case in house	1
12	51	F	0	...	5 "	Case in house	0
13	43	M	Yes	None	3 "	Hospitalization during disease	0
14	13	F	Yes	None	3 "	Hospitalization during disease	0
15	62	M	Yes	22 yrs.	7 "	Examination as food handler	0
16	43	F	0	...	6 "	Hosp. for G.B. symptoms	0
17	65	F	Yes	27 yrs.	3 "	Hosp. for unrelated illness	0
18	59	F	0	...	10 "	Case in house	1
19	50	F	Yes	None	3 "	Hospitalization during disease	0
20	72	F	Yes	40 yrs.	9 "	Case in house	1
21	23	F	Yes	None	2 mos.	Hospitalization during disease	0
22	47	F	Yes	22 yrs.	3 "	Examination as food handler	0

Subjects of the Investigation. In the summer of 1935, 31 carriers were listed with the Department of Public Health of Philadelphia. Of 22 available for study,* 16 were women (Table 1). The average age was 51.7 years, the youngest being 13 and the oldest, 77 years. Only 13 gave

* Dr. G. E. Johnson, of the Division of Communicable Diseases of the Department of Public Health, very kindly supplied us with the names of the carriers and encouraged them to coöperate.

a history of typhoid fever, and an average of 14 years had elapsed between the illness and discovery of the carrier state. Except for those recognized during hospitalization for their primary illness, the discovery that they were carriers was usually made following the occurrence of a case of typhoid fever in the household. Two subjects, however, were identified as carriers by routine feces examinations when they applied for positions as food handlers, each 22 years after the original illness. In 2 other instances the discovery was made accidentally when the patients were treated for unrelated complaints. The entire group had been registered with the Department of Public Health for an average of 4.1 years; one-half were known to have been responsible each for 1 or more cases of typhoid fever.

Methods of Study and Treatment. In each patient a physical examination was made, a history was taken, and feces and urine were cultured. Duodenal drainage was carried out on those whose feces contained typhoid organisms. Specimens of fasting duodenal fluid and of concentrated "B" bile, obtained following the instillation into the duodenum of warm olive oil, were collected and cultured separately. Roentgen examination of the gall bladder was made in each patient following the oral administration of sodium tetraiodophenolphthalein. All subjects who were not suitable for cholecystectomy or who refused it were given the opportunity of choosing Roentgen ray therapy, and 12 availed themselves of this procedure. The treatment, which duplicated in every important respect the procedures employed by Gulbrandson,[2] consisted of one or two courses of deep therapy, 330 to 800 R, given at 2- to 4-month intervals.* Treatment was directed over the kidneys or the gall bladder, depending upon the location of the infection as indicated by the previous studies. Following radiation repeated cultures of feces and of urine were made, and also in certain instances a culture of the bile.

Two individuals submitted to surgery, the preliminary studies having been carried out as described. At operation† cultures were made from gall-bladder bile, from the submucous and the muscular coats of the gall bladder and from the interior of calculi removed from the gall bladder. Cultures of feces and of duodenal fluid have been obtained at frequent intervals for a period of 1 to 2 years since operation.

Results of Study and Treatment. In Table 2 are presented the results of Roentgen examination of the gall bladder, of cultures of duodenal fluid and of cultures of feces and urine before therapy was instituted. Positive stool cultures were obtained from 17 of the 22 persons. In all of them Roentgen examination of the gall bladder revealed impaired function, and culture of the duodenal fluid was positive. It was an interesting fact that in 3 a positive culture was obtained only from the concentrated bile. Symptoms suggestive of gall-bladder disease were present in only one-third.

Of the 22 subjects 2 were urinary carriers. In 3 others positive urine cultures were believed to be the result of contamination at the time of collection, and these persons were considered fecal carriers. From 3 no positive cultures were obtained, although these later submitted positive stool specimens to the Health Department.

* Further details of procedure were: For subjects receiving 300 to 650 R, voltage 135 kv.—50 cm. distance—0.25 mm.cu. + 1 mm. al. filtration. For subjects receiving 800 R, voltage 165 kv.—50 cm. distance—0.5 mm.cu. + 2 mm. al. filtration.

† Dr. I. S. Ravdin performed the cholecystectomy in each instance. We are indebted to him for his coöperation.

The results of treatment with Roentgen ray are seen in Table 3. In no instance did cultures of feces or urine become consistently negative after this treatment and culture of duodenal fluid, obtained from 2 patients (Cases 3 and 4), was positive when examined 6 months after conclusion of treatment.

Patients 21 and 22 (Tables 1 and 2) submitted to cholecystectomy after completing the preliminary studies. In both of these the

TABLE 2.—RESULTS OF CULTURES, FINDINGS ON ROENTGEN EXAMINATION OF THE GALL BLADDER AND FREQUENCY OF GALL-BLADDER SYMPTOMS IN 22 TYPHOID CARRIERS.

Patient.	Cultures.				Roentgen examination of gall bladder.†	Gall bladder symptoms.
	Feces.	Urine.	Duodenal fluid.*			
			No. 1.	No. 2.		
1	0	+	..	..	Neg.	0
2	0	+	..	..	..	0
3	+	0	+	+	Abn.	+
4	+	0	0	+	Abn.	+
5	+	0	..	..	Abn.	0
6	+	0	+	+	Abn.	++
7	+	0	+	+	Abn.	
8	+	0	+	+	Abn.	0
9	+	0	0	+	Abn.	0
10	+	+	+	+	Abn.	
11	+	0	..	..	Abn.	0
12	+	0	0	+	Abn.	++
13	+	0	+	+	Abn.	0
14	0	0	0	0	Neg.	0
15	0	0	0	0	Abn.	0
16	0	0	0	0	Abn.	+++
17	+	0	..	..	Abn.	0
18	+	0	..	..	Abn.	0
19	+	+	..	..	Abn.	0
20	+	+	..	..	Abn.	0
21	+	0	+	+	Abn.	0
22	+	0	+	+	Abn.	+++

* Specimen 1 consisted of fasting, amber bile; Specimen 2 was obtained after olive oil and consisted of concentrated bile.

† Neg. indicates functioning gall bladder; Abn. indicates abnormal function.

TABLE 3.—ROENTGEN RAY THERAPY AND RESULTS OF CULTURES MADE FOLLOWING THIS THERAPY.

Patient.	First Roentgen series, dosage.	Cultures after 1st course of treatment.		Second Roentgen series, dosage.	Cultures after 2d course of treatment.	
		Feces.	Urine.		Feces.	Urine.
1	650 R*	0	+			
3	650 R	+	+	650 R	+	0
4	650 R	+	0	600 R	+	0
5	520 R	+	0	600 R	+	0
6	650 R	+	0	650 R	+	0
7	800 R	+	+	800 R	+	0
8	650 R	+	0	650 R	+	+
9	800 R	+	0			
10	800 R	+	0			
11	800 R	+	0			
12	330 R	+	0			
13	800 R	+	0			

* Treatment was directed over both kidneys in this patient; in others over the gall bladder.

culture of duodenal fluid prior to operation was positive and Roentgen examination of the gall bladder revealed impaired function. At operation positive cultures were obtained from gall-bladder bile, from the mucous membrane of the gall bladder and from the interior of calculi. In Patient 22 a culture from the muscular coat was also positive. After operation cultures of the duodenal fluid and of feces have been negative in each instance from the third post-operative day to 13 months after operation, examinations having been made at intervals of approximately 3 months during this time.

Conclusions. 1. Evidence of involvement of the gall bladder was obtained either by duodenal drainage or by Roentgen examination in all of 17 typhoid carriers whose stool cultures were positive. Infection was demonstrated only in the urinary tract in 2 others.

2. Irradiation directed over the gall bladder in 12 carriers failed to destroy the organisms as judged by persistently positive cultures of bile and feces. This therapy was also ineffective in the one urinary carrier treated.

3. Surgical removal of the gall bladder in 2 carriers permanently removed the focus of typhoid infection.

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ACUTE PANCREATITIS: A MEDICAL PROBLEM.*

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Despite the fact that the surgical treatment of acute pancreatitis has not appreciably lessened the mortality rate in the past 50 years, the dominant medical opinion today concerning the treatment of this disease is that it remains a serious surgical problem. There is, however, considerable disagreement as to the best surgical approach. Some incise the pancreatic capsule, others drain the common duct; some drain the gall bladder, others remove it; still others do various combinations of the above. Similar confusion exists as to the optimum operative time. Whereas some authorities believe that

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the deplorably high death rate can be lowered only by immediate operation, others recommend delaying the operation for several hours until the initial shock has passed. Still others advise the so-called interval operation in which surgery is deferred for from 4 to 8 days. The confusion still extant as to the relative merits of the various operative procedures and as to the optimum operative time undoubtedly remains unresolved because of the monotonously high mortality rate common to all of them.

The most recent tendency in the treatment of acute pancreatitis, abstinence from operation, represents a radical departure from the generally accepted surgical attack on the disease. This, on first thought, appears to confuse the problem further, but may ultimately clarify and simplify it. Hartlieb[7] is absolutely opposed to the prevailing idea of surgical intervention. Whereas he had in years past operated on 23 patients with 12 deaths, the usual mortality rate, in a later group of 7 cases, treated expectantly, 5 recovered and 2 died. Nordmann[11] treated 9 patients with acute pancreatitis conservatively with 7 recoveries. Mikkelson[10] reported conservative treatment of 39 cases of acute pancreatitis with the amazing mortality rate of only 7.5%. He believes that it is irrational to incise the pancreatic capsule, as incision of such a peritoneal covering cannot possibly relieve secretory tension. It is Walzel's[14] opinion that operation should only be considered in those cases in which a surgical condition, such as a ruptured peptic ulcer, cannot definitely be excluded and that if, at operation, an acute pancreatitis is found, the abdomen should be closed. Hofhauser[8] stresses the importance of differentiating between necrosis of the gall bladder and necrosis of the pancreas because the treatment is surgical in the former and conservative in the latter. Doubt that operation can appreciably lessen the necrosis of pancreatic tissue with its attendant release of toxins is expressed by Archibald and Kaufman.[1] In their experiments with acute pancreatitis in dogs, Cook and Whipple[4] showed that the pancreas has unusual power of recuperation if it is let alone behind a closed peritoneal cavity.

Data. The above reports stimulated us to analyze the records of patients with acute pancreatitis who were admitted to this hospital during the past 3 years (Table 1). The 16 unselected cases were comprised of 10 males and 6 females. The youngest patient was 32 years of age and the oldest 70 (average 46). Patients 1 to 4 were operated on either on the first or second day of admission, with 3 deaths and 1 recovery. Patients 5 to 8 were operated on from 8 to 13 days after admission and after the acute symptoms had completely subsided. These patients were operated on only because mild signs of gall bladder disease, such as tenderness in the right upper quadrant, persisted. Of these, all showed evidence of acute hemorrhagic pancreatitis on laparotomy. In only 1 was the capsule incised. In the remaining 4 cholecystectomy was performed. The

operation in no case was deemed essential for the acute pancreatitis itself; in fact, as stated above, the symptoms of shock, abdominal pain, vomiting and temperature had completely disappeared. From the standpoint of acute pancreatitis, these cases are considered as non-operative. Of Patients 9 to 16 who were not operated on at all, 4 recovered and 4 died. The deaths occurred in Case 11, a man of 70, the oldest patient in the group; in Case 14, who had anuria for 24 hours and a urea nitrogen of 100 mg. per 100 cc. of blood; and in Case 15, who had anuria for 2 days and necropsy

TABLE 1.—RESULTS IN 16 CASES OF PANCREATITIS.

Case.	Sex.	Age (yrs).	Oper. No. days after admission.	Type of operation.	Oper. findings.	Result.	Autopsy.	Diastase.	Ser. lipase.	Hyperglycemia mg. per cent.
1	F.	42	1	G. B. drained	Sero-sanginous fluid, fat necrosis	Died	+	..	..	352
2	M.	49	Same	G. B. drained	Hem. panc., fat necrosis, gall bladder stone	Died	+	1:128	..	260
3	F.	36	1	Cap. incised	Fat necrosis, edem. and hem. pancreatitis	Died	..	..	..	240
4	M.	41	Same	Cap. incised	Edem. pancreatitis, free sang. fluid	Recovered				
5	M.	43	10	G. B. removed	Fat necrosis, hem. fluid edem. panc.	Recovered	..	1:200	..	190
6	M.	59	8	G. B. removed	Cholelithiasis, hem. pancreatitis, fat necrosis	Recovered	..	..	..	280
7	F.	53	12	G. B. removed panc. incised	Cholelithiasis, fat necrosis, hem. fluid	Recovered	..	1:256	..	330
8	F.	42	13	G. B. removed	Gangrenous cholecystitis; hem. pancreatitis	Recovered	..	1:128	..	210
9	F.	38	10	G. B. removed	Calc. cholecystitis, fat necrosis, free fluid	Recovered				
10	M.	44	..	..	...	Recovered	..	1:512	..	195
11	M.	70	..	..	...	Died	+			
12	M.	46	..	..	...	Recovered	..	1:256		
13	F.	45	..	..	...	Recovered	..	1:1024	..	310
14	M.	40	..	..	...	Died	+	..	..	200
15	M.	64	..	..	...	Died	+			
16	M.	32	..	..	...	Recovered	..	1:521	2.6	

findings of a severe and extensive nephrosis. The criteria for the diagnosis of acute pancreatitis in the 4 patients who recovered without operation were the typical clinical features plus markedly elevated urinary amylase estimations. The clinical features alluded to conformed to a rather characteristic pattern of severe right upper quadrant pain which radiated to the left, marked distention, vomiting, shock and a mild elevation of temperature. In 3 patients we were able to demonstrate a small amount of fluid in the chest, presumably due to a pleural reaction by extension from the pancreas. Mention should be made that those cases not operated on, or operated on late, were in no way milder clinically than those on whom operation was performed early. When the results in Pa-

tients 5 to 16 are grouped together under the non-operative treatment of this disease, it will be seen that 9 of the 12 patients recovered, whereas 3 of the 4 patients subjected to the additional burden of an early operation succumbed.

The idea that surgery in acute hemorrhagic pancreatitis should be abandoned coincides with the recent interesting work by Duff and Rich[12] on the pathogenesis of this disease. They found in 13 of 24 pancreatic glands studied that the disease is due to obstruction of the pancreatic ducts by a metaplasia of the ductal epithelium. This metaplasia, patchy in distribution, is a localized proliferation which projects into the ducts and partially or completely occludes their lumina. The ductules and acini immediately behind the obstructed ducts become greatly distended and their thinned out walls become easy to rupture. The cause of acute hemorrhagic pancreatitis resides often, therefore, in the gland itself and not in factors external to it such as gall stones, spasm of the sphincter of Oddi or lymphatic infection. If this view of the pathogenesis of acute pancreatitis is correct, it can readily be seen that the surgeon could not possibly know, considering the scattered nature of the lesion, in which lobules the obstructed ducts may be, and even if he did, the necessary multiple incisions into individual lobules could only increase the hazards of necrosis.

In any discussion of treatment a few words about diagnosis are in place. As will be seen in Table 1, 8 estimations of urinary diastase were made, all of which were definitely elevated. We regard this test, along with Foged,[6] Rost,[13] McCaughan[9] and others, as exceedingly helpful. Its ease of performance should lead to its more general use in all cases of suspected acute pancreatitis. It is true that elevation of the urinary diastase has been observed in kidney disease, diabetes mellitus and peptic ulcer, but in none of these conditions are more than moderate increases encountered. The normal index of diastasuria oscillates between 6 and 30 units. Table 1 shows how much higher the figures rise in acute pancreatitis. Even those who do not think the test specific admit its value when interpreted in the light of clinical findings.

Serum lipase estimation, a relatively new test, may supersede the diastase test in accuracy as a valuable diagnostic aid in acute pancreatitis. Cherry and Crandall[5] showed that lipase in normal sera exists in minute amounts and that it is increased markedly after ligation of the pancreatic ducts. Comfort and Osterberg[3] think the increase in serum lipase good evidence of disturbed pancreatic function especially when correlated with the clinical picture. According to Bernhard,[2] the increase in serum lipase subsides more slowly than the increase in urinary diastase. In our own series, we performed the test only once with, we believe, a correct result.

The point we wish to stress is that a diagnosis of acute pancreatitis can be made without operation. The clinical aspects alone are

often unmistakable. However, when these are insufficiently clear, we have now two fairly reliable tests which can be easily and quickly done, to help clarify the diagnosis. We believe an early diagnosis important so that surgery may be avoided.

Summary and Conclusions. The operative mortality of acute hemorrhagic pancreatitis remains uniformly high, which probably accounts for the existing disagreement concerning the best operative approach and the optimum operative time. Recent reports on the non-operative treatment of this disease show a lower mortality rate. We present 16 cases of acute pancreatitis in which 4 were operated on with 1 recovery and 12 were not operated on for the pancreatitis with 9 recoveries. Diastase and lipase estimations are of considerable value in the diagnosis of suspected pancreatitis. It is felt that further trial with conservative therapy in acute hemorrhagic pancreatitis is warranted.

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CLINICAL OBSERVATIONS ON THE TREATMENT OF PNEUMONIA AND EMPYEMA BY SOME QUININE DERIVATIVES, ESPECIALLY HYDROXYETHYLAPOCUPREINE.*

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In a previous report[9] we indicated that hydroxyethylapocupreine was of considerable interest because of its low toxicity for mice and its relatively high antipneumococcic power, as compared with other

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quinine derivatives. An experimental study[2] in dogs was of further interest in regard to hydroxyethylapocupreine in that this compound was found to be free from damaging effects on the retina, and therefore did not produce blindness. On the other hand, optochin and ethylapocupreine did cause blindness in these experiments, while apocupreine did not. It is a well known clinical fact that the use of optochin in the treatment of pneumonia cases has been associated at times with the temporary loss of vision. It is this untoward result that is probably responsible for this interesting chemical being withdrawn from the therapy of pneumonia by most physicians. In the past, we have seen a moderate number of early pneumonia cases treated with optochin in the usual small therapeutic dosage with the result that the mild cases recovered while the toxic cases did not appear to be affected. The latter, when observations were made, were usually the positive blood culture cases. Moore and Chesney[10] and Solis-Cohen[11] many years ago made careful experimental and clinical studies on optochin and quinine. We refer the reader to their work. In the years 1930–1931 we decided it would be of value to prove whether optochin in large dosage did have the power of favorably altering the course of toxic pneumonia cases. We observed 4 patients. All had positive blood cultures, both in the broth flasks and on the blood agar plates. The highest colony counts, respectively, were 6, 8, 45 and 260. These cases were given 60 gr. of optochin per day for 3 to 5 days. They all recovered. Two (cases with 6 and 260 colonies) showed no visual disturbance, while the other 2 developed blindness from which they recovered good vision in the course of 2 months. Further, at this time, we also treated a single case of pneumococcic endocarditis, which as far as we know is invariably fatal, with very large doses of optochin. This patient had, as is common for practically all cases of pneumococcic endocarditis, pneumococci in the blood with high colony counts. He was given 90 gr. of optochin per day for 3 days. The chemical was discontinued for 2 or 3 days and then given again in the same dosage for the same length of time. This was repeated four times so that the patient received about 1000 gr. He never showed any visual disturbance, indicating that the blindness due to the quinine derivatives is probably an idiosyncrasy. The blood cultures would be sterile after the second day of treatment, but the organism returned when the optochin was stopped. The patient died on the 35th day of his illness and the autopsy confirmed the pneumococcic endocarditis.

Later, in 1932–1934, we treated a much larger series of positive blood culture cases with ethylapocupreine. The dosage was from 40 to 60 gr. per day and it was continued from 3 to 4 days. Naturally in dealing with positive blood culture cases there were many of the total number that did not show the pneumococci in the blood until after the fourth day of the disease. Negative blood culture

cases were not treated. In this group of 24 cases there were 10 recoveries and of the cases which recovered, 4 showed high colony counts on the blood agar plate, 15, 21, 32 and 377, respectively. Five out of the 24 cases developed blindness. One of this group of 5 died, while the remaining 4 regained good vision in periods varying from 1 to 3 months.

From these clinical observations with optochin and ethylapocupreine we were impressed with two facts. The first one was that the visual disturbance, which in our cases was total blindness for several days followed by partial loss of vision for a number of weeks but with ultimately good vision returning, renders such chemical compounds absolutely impossible to use in clinical medicine. The second fact was that we had very suggestive evidence that the blood stream could be freed from pneumococci and that some of the patients recovered from their pneumonia if a sufficiently large enough dosage of chemical be given. The desirability, therefore, of developing a quinine derivative devoid of the visual damaging factor but with the pneumococcidal power not impaired naturally was obvious.

For part of the winter of 1934–1935 we used apocupreine which by animal and *in vitro* tests had very little toxicity and fair antipneumococci power. This chemical compound was discarded after a few months' trial on 20 cases of pneumonia. We saw practically no evidence in the positive blood culture group that were treated in this series that apocupreine had any effect on the course of the disease. This preparation, however, produced no blindness and could be given in very large dosage, 120 gr. per day for 4 or 5 days. It is possible that this chemical is altered in the human body and its antipneumococcic power is subsequently lost.

Hydroxyethylapocupreine was first used in the treatment of pneumonia cases in 1935–1936. It was given in capsule by mouth in divided doses, and the usual dose at that time was 60 gr. per day. A few cases had more. It was soon noted that no evidence of visual disturbance was to be observed, and in the following year this finding has been confirmed. After treating about 200 cases there has not been a single example of visual disturbance, which agrees with our experimental study on dogs previously mentioned. In the first year there was no nausea or vomiting associated with the use of the hydroxyethylapoquinine, and on only one occasion did ringing of the ears appear, after 600 gr. had been taken. In the year 1936–1937, however, a good deal of nausea and vomiting was seen, but we feel fairly certain that these symptoms were characteristic of the epidemic influenzal infection which was prevalent, as frequently the non-chemically treated cases had nausea and vomiting, usually during the first few days of illness. It is quite true that in the presence of nausea and vomiting most medication by mouth will increase these disagreeable symptoms, and this undoubtedly hap-

pened during the past year with our cases of pneumonia treated with the chemical.

The dosage of hydroxyethylapocupreine during the past year (1936–1937) was very much larger than during the first year (1935–1936). This was partly due to the fact that in the first year the chemists at the Mellon Institute were able to get only a 5% yield in production. However, in the summer of 1936, Dr. Butler increased the yield of hydroxyethylapocupreine from quinine by a new process to 40%. Consequently for the past year we have had an adequate amount to use, and accordingly increased the dosage. Fifteen grains every 3 hours, day and night, has been the routine dosage. From 400 to 900 gr. in the course of a week has been frequently given. During the past year we have given intravenous injections of the chemical to a certain number of the more toxic cases. Fifteen grains in 50 to 75 cc. of distilled water can be injected into the vein safely every 3 or 4 hours. We have frequently given 60 gr. by mouth and 90 gr. intravenously per day in divided doses.

Hydroxyethylapocupreine in the form of the dihydrochloride was first used, but this salt is quite acid and probably accounted for the almost constant thrombosis of the veins at the point of injection. In the past few weeks we have substituted the monohydrochloride which is almost a neutral solution and in a limited experience have seen no local thrombosis of the veins of the arm. The monohydrochloride solution is readily made by dissolving 15 gr. (1 gm.) of the hydroxyethylapocupreine dihydrochloride in 100 cc. of distilled water (a 1% solution) and to this solution adding slowly about 2.5 cc. of normal sodium hydrate. The solution becomes milky at first but clears when the monohydrochloride stage is reached.

No intravenous injections were used in the first year (1935–1936) and this fact in addition to the small dosage given by mouth probably accounts for the greater mortality seen in our first than in the second year.

There was only one instance when a reaction associated with a fall in blood pressure followed the intravenous injection. We have so far met with no example of a definite alarming allergic response to the hydroxyethylapocupreine. Ringing in the ears was noted once during the first year and twice this year in patients who had taken large doses. It was only slight and stopped with the discontinuance of the chemical. After large dosage in a few individuals we have noted a fine skin eruption which may be due to the hydroxyethylapocupreine. It caused no discomfort and was very temporary in character. We do not believe the nausea and vomiting seen at times this year can be a manifestation of drug sensitivity, as it was not present last year and the symptoms were frequently noted in non-chemically treated cases this year. Of course, there may be cases that will not be able to take this chemical. Certainly, it appears to be entirely free from any of the untoward reactions

that are associated with quinine, optochin and ethylapocupreine, even when the hydroxyethylapocupreine is given in much larger doses.

It is our belief that the chemical should be taken by mouth as soon after the chill or onset as possible and continued as long as necessary. The intravenous method is for the more toxic cases, especially those with positive blood cultures. Probably very little benefit can be hoped for in cases after the fourth day of the disease as is true for specific serum.

TABLE 1.—MORTALITY FIGURES.

	Treated cases.		Untreated cases.	
1935–1936	46	17 deaths (37%)	48	20 deaths (42%)
1936–1937	100	27 " (27%)	46	29 " (63%)
1935–1937	146	44 " (30%)	94	49 " (52%)

Mortality According to Types.

	Types.	Treated cases.	Deaths.	Untreated cases.	Deaths.
1935–1936	I	4	2 (50%)	8	1 (12%)
	II	10	6 (60%)	3	2 (67%)
	III	4	3 (75%)	7	6 (86%)
	Group IV	28	6 (21%)	30	11 (37%)
1936–1937	I	13	5 (38%)	4	2 (50%)
	II	19	8 (42%)	1	1 (100%)
	III	15	9 (60%)	8	7 (87%)
	Group IV	48	5 (10%)	12	7 (58%)
Unknown		5	0 (0%)	21	12 (57%)

Mortality as to Types in the 44 Deaths in Treated Cases.

1935–1937	Type I	7 deaths	(16%)
	II	14 "	(32%)
	III	12 "	(27%)
	Group IV	11 "	(25%)

(Types IV, VII, VIII, X (2), XVIII, XX, XXVI, Group IV unclassified. (3).)

In the above table the mortality figures for the first year, 1935–1936, show little difference between the treated and non-treated. In this first year, the untreated cases were frequently early cases, while in the year 1936–1937 the untreated cases were nearly all beyond the fourth day of the disease. Therefore, they are not to be considered as true control cases. The mortality in the second year is lower than the first. (The normal mortality in our hospital ward for 100 non-specifically treated cases has been about 45%. In 1935, Pittsburgh had 161 deaths from pneumonia per 100,000; in 1936, 193 per 100,000; and 1937 will probably be higher due to the epidemic of influenza, as in the first 4 months of the year 1937 there were 84 more deaths from pneumonia and influenza than during the same period of the previous year.) The mortality according to types shows that the three fixed types are the highest with a lowering of the figures during the past year. The cases in regard

to type mortality were too few in the first year to be accurate. The large number of unknown types in the untreated series of 1936–1937 was due to a combination of the following circumstances: no sputum, late cases, a few outside cases and cases on other services.

TABLE 2.—CASES TREATED BUT NOT INCLUDED IN OUR LISTS.

1. Five died with insufficient treatment, 3 being less than 1 day and 2 less than 2 days. Of the latter, 1 had coronary thrombosis while the other had mitral stenosis with fibrillation and circulatory failure.
2. There were 25 in which the final diagnosis of pneumonia could not be made: 22 recovered, 3 died, deaths being due to lung abscess, coronary thrombosis and bronchogenic carcinoma of lung.
3. Four postoperative pneumonias were treated, with 3 recoveries and 1 death.
4. No children were included.

Some of the recovered cases of Section 2 were patients to whom the chemical was given almost immediately or within a very few hours after the chill. Prompt cessation of their symptoms and absence of signs which included Roentgen rays for all hospital cases made a positive diagnosis of pneumonia impossible. This group, however, represents a most interesting picture and there should be no difficulty in the future in collecting many cases where the chemical has been given very shortly after the chill. This will be applicable to hospital pneumonia only occasionally, but many cases in the homes are seen by their physician at the earliest stages of the disease and this group should be very instructive.

TABLE 3.—ANALYSIS OF SOME OF THE 27 FATAL TREATED CASES (1936–1937).

Staphylococcus empyema and bacteremia	1
Streptococcus hemolyticus bacteremia	1
Delirium tremens	2
Late cases—sixth and eighth days	2
Sudden death—end of third day; temp., 98.8° F.; pulse, 100 (Coronary ?)	1
Pneumonia associated with severe epidemic influenza	6
	13

This table is given not with the intention of excusing the mortality during the past year but to call attention to the fact that mixed infection in our opinion undoubtedly played a part in the mortality. Pneumococcus was present in all of the fatal cases in addition.

TABLE 4.—INCIDENCE OF H. INFLUENZÆ AND STREP. HÆMOLYTICUS IN SPUTUM.

Month.	Sputum specimens.	H. influenzæ.	Strep. hæm.	H. infl. and Strep. hæm.
December, 1936	22	1 (4%)	0	0
January, 1937	44	18 (41%)	9 (20%)	3
February, 1937	23	7 (30%)	5 (21%)	1
March, 1937	25	15 (60%)	7 (28%)	4
April, 1937	16	8 (50%)	4 (25%)	1

The epidemic influenza appeared during the last week of December, 1936. The above table indicates the increase in the *H. influenzæ*

and the *Strep. hæmolyticus* during the past winter. This was done by making blood agar and chocolate agar plates from the sputum, and the above records are from cultures, not from direct smears of the sputum. The incidence of both of these organisms is far above our normal findings for a non-epidemic year. The chart adds further proof of mixed infection in the pneumonias of the past winter.

TABLE 5.—ANALYSIS OF PNEUMOCOCCUS TYPING.

Type.	1935–1936.		1936–1937.	
	No. of cases.	Per cent.	No. of cases.	Per cent.
I	15	15.0	17	14.1
II	13	13.0	20	16.6
III	14	14.0	23	19.1
IV	3	3.3	5	4.8
V	..	..	5	4.8
VI	1	1.1	1	0.9
VII	7	7.7	7	6.7
VIII	9	9.9	6	5.7
IX	3	3.3	1	0.9
X	5	5.5	3	2.8
XI	2	2.2		
XII	1	1.1	2	1.9
XIII	1	1.1	1	0.9
XIV	2	2.2	1	0.9
XV				
XVI				
XVII				
XVIII	2	2.2	1	0.9
XIX	1	1.1	1	0.9
XX	3	3.3	1	0.9
XXI				
XXII	..	..	1	0.9
XXIII				
XXIV	..	..	1	0.9
XXV	6	6.6	1	0.9
XXVI	1	1.1		
XXVII	1	1.1	2	1.9
XXVIII	1	1.1	1	0.9
XXIX	..	..	2	1.9
XXX				
XXXI	..	..	1	0.9
XXXII				
(Group IV unclassified)	9	9.9	16	13.3
	100		120	

The small number of Type I cases has been noted for several years in Pittsburgh in all laboratories where typing has been done. It is interesting that Type III has been so relatively frequent during the past 2 years.

There was a definite difference in the mortality of the treated and untreated series, both in the negative and positive blood culture cases in the combined years of 1935–1937. The untreated series are not true controls, in that they were late cases, especially during the year 1936–1937. We would emphasize that 19 treated cases with positive blood cultures recovered, while there were only 4

TABLE 6.—ANALYSIS OF BLOOD CULTURES (1935–1936).

	Treated cases.				Untreated cases.			
B. C.	Cases.	D.	R.	Mortality.	Cases.	D.	R.	Mortality.
Neg.	24	3	21	12%	36	11	25	31%
Pos.	22 (48%)	14	8	64%	12 (25%)	9	3	75%
1936–1937.								
Neg.	63	10	53	16%	27	12	15	44%
Pos.	25 (28%)	14	11	56%	14 (34%)	13	1	93%
Combined Figures (1935–1937).								
Neg.	87	13	74	15%	63	23	40	36%
Pos.	47 (35%)	28	19	59%	26 (29%)	22	4	85%

recoveries in the non-treated group. The 4 untreated positive blood culture cases that recovered (Types I (2), II, XXV) had no colonies on the blood agar plate, the pneumococci being present only in the broth flasks. The high mortality figures for the negative blood culture cases in the untreated group is difficult to explain, but two factors may play a part: (1) Failure to take blood cultures up to the time of death (some of these cases were not under control) and

TABLE 7.—ANALYSIS OF 19 POSITIVE BLOOD CULTURES IN RECOVERED CASES (1935–1936).

Name.	Type.	No. pos. B. C.	Colony counts.
Cirelli	II	1	0
Johnston	VIII	2	8, 4
Evans	VIII	5	2, 0, 2, 1, 0,
Yeckley	X	2	0, 0
Hanley	VIII	2	0, 0
Dugan	XX	3	1, 38, 0
McKinney	XII	2	0, 0
McDaniel	VIII	1	0
1936–1937.			
Rankin	I	1	0
Ferguson	VIII	1	0
Robertson	IV	1	0
Gillespie	Group IV	1	0
Cain	II	1	0
Fabiani	II	1	0
White	VIII	1	0
Deferris	IX	1	0
Bianco	V	5	1, 418, 260, 0, 4
Culver	VII	3	231, broth pos. twice but no plates made
Patton	II	13	54, 4, 4, 48, 67, 28, 10, 58, 10, 0, 5, 2, 0

thus classifying cases in the negative group when they really may have had a bacteremia; (2) during the past winter with the large amount of mixed infection, prolonged clinical courses from 12 to 20 days were not infrequent and more cases were noted dying with negative blood cultures than formerly.

There were 4 instances in the above 19 recovered positive blood

culture cases in which the colony counts were above 15 per cubic centimeter, while 9 showed multiple positive cultures. In the above chart 0 means that there were no colonies on the plate, but the broth was positive. It is our belief that the mortality figure in 100 chemically treated positive blood culture cases (cases not later than the fourth day) should give a fairly accurate idea as to the value of this method of therapy. This could be controlled further by comparing a similar series of positive blood culture cases, with and without specific serum, from other hospitals in Pittsburgh.

TABLE 8.—MORTALITY FIGURES ACCORDING TO DAY OF DISEASE WHEN FIRST TREATED (1935–1937).

Day.	Cases.	Deaths.	Positive B. C.		Types I, II, III.	
			No.	Deaths.	No.	Deaths.
First . . .	50	13 (26%)	13 (26%)	4 (31%)	16 (32%)	8 (50%)
Second . .	50	17 (34%)	16 (32%)	11 (69%)	27 (54%)	14 (51%)
Third . . .	21	1 (4.7%)	4 (19%)	1 (25%)	8 (38%)	1 (12%)
Fourth . .	20	10 (50%)	12 (60%)	9 (75%)	12 (60%)	8 (67%)
Fifth plus . .	5	3 (60%)	2 (40%)	2 (100%)	2 (40%)	2 (100%)

77% of the 13 fatal cases treated on first day died within 5 days of onset.
23% of the 17 fatal cases treated on second day died within 5 days of onset.

We would call attention to the low mortality of the cases first treated on the third day. The 21 cases included 8 in 1935–1936 and 13 in 1936–1937. The single death occurred in the last year. The percentage of the three fixed types (the more virulent forms) in the third-day group was higher than those cases of the first day, while the positive blood culture percentage was somewhat lower than the first-day cases. The duration of the pneumonia in the fatal cases treated on the second day was considerably longer than for those treated on the first day. It is possible that there may be a common explanation for the low mortality in the third day and the difference in duration of the disease in the fatal cases of the first and second days. This should be easily proved during the coming year when larger numbers are available.

We have previously mentioned that mixed infection was present to a considerable extent during the past winter and have shown some bacteriologic evidence as indicated by the cultures made from the sputum of the pneumonia cases. Autopsy findings this year confirmed the clinical fact that we have had epidemic influenza as a background for the pneumonias. Although much less in number, practically all of the autopsy findings of the 1918 epidemic were reproduced this past winter. Three cases showed typical Zenker's degeneration of muscle as was so accurately described by Klotz[5] in his pathologic studies of the influenza epidemic in Pittsburgh in 1918. The wet hemorrhagic lungs were fairly frequently observed and delayed resolution with small multiple abscess formation was also seen.

From the clinical side several unusual features of the pneumonias were noted. At the onset nausea and vomiting was not only common but it was very severe in many cases and at times persisted

for 3 or 4 days. This condition was not seen in 1935–1936. An occasional cyanotic case of the 1918 type was encountered but we saw no evidence of the leukopenic state that was so frequent in the previous epidemic. A few low white counts were noted in the pneumonias this year, but they were usually found in chronic alcoholics. The delay in the appearance of typical signs of consolidation, prolonged periods of depressed breathing over the involved lobe, and the presence of widely diffused râles through the lung were also noteworthy.

Probably one of the most characteristic features of the pneumonias this year was the prolongation of the febrile course and signs of delay in resolution of the process. In 1935–1936, 13% of the recovered treated cases showed fever for over 15 days, while in 1936–1937 the percentage was 22. In the untreated recovered group, during the first year 7% had fever for over 15 days, but in the second year 47% of the cases showed a prolonged febrile reaction.

It might also be added that streptococcic hæmolyticus empyema in adults, following a pneumonic course, has been more in evidence than our records would indicate for many years. We hope that the influenza epidemic of the past winter represents the peak of the infection and not a forerunner of the coming year, as its virulence next year would need very little enhancing to cause a most serious disease.

In 1922, Gralka[4] reported the first case of pneumococcic empyema treated by the injection of optochin into the pleural sac. His cases were in children, and in fact all of the subsequent literature on this problem deals with empyema in children. Gralka's first case occurred in 1920. Kolmer and Sands[6] drew attention to this subject in 1921 when they reported on some experimental studies on empyema in guinea pigs which were treated effectively by injections of optochin. Woringer,[12] Leitner,[7] Bussel and Hirszfeld,[1] Lowenburg,[8] Edeiken[3] and others have reported that optochin was of value in the treatment of empyema in children. The total number of cases has not been large and one is surprised that this method of treatment has received so little attention. We have not seen any record of treatment of pneumococcic empyema in the adult by this method. The fear of visual disturbance by optochin and the fact that recognized empyema in the adult carries a low mortality with the usual surgical methods of approach probably account for the lack of interest in the chemical therapy for this condition.

For the past 7 years we have treated most of our empyemas with one of the quinine derivatives, although in the first 2 years when we used optochin in a dilution of 1 to 400, tubes were inserted between the ribs into the empyema sac and the optochin solution was left in the cavity. This was repeated daily. The duration of the empyema was shortened considerably. Ethylapocupreine was used in the same way at first, but later we injected a 0.5% solution,

never more than 100 cc., into the pleural sac after the aspiration of as much of the purulent fluid as possible. This was done 3 or 4 times in the course of a week or 10 days. Only occasionally was it necessary to put tubes into the cavity. It was this closed method that was used by the previous writers mentioned above. The dosage of optochin or ethylapocupreine was far below the toxic dose which produces blindness and the method was therefore safe. We treated but a small number of cases in this manner, 2 or 3 per year.

However, since 1935 we have injected the hydroxyethylapocupreine in a 1 or 2% solution and in this period have seen about 15 cases of empyema. It has been very effective in our hands. The course of the empyema is shortened, at times to 1 or 2 weeks, and the method is much easier for the patient, in that there is no rib resection or introduction of tubes between the ribs into the pleural sac. We have had 1 case of empyema on the left side with a pericardial rub which persisted for 5 days, but which disappeared as did the empyema in the course of 10 days after 4 injections of 100 cc. of a 2% hydroxyethylapocupreine. It was a Type I infection.

Our procedure is as follows: Aspirate the pus and prove that it is pneumococcus by cultural methods, as this chemical does not affect the streptococcus. Inject 100 cc. of a 1 or 2% solution of the drug after removing as much of the empyema pus as possible. Obviously, if only 50 cc. of pus is removed, the amount of the chemical solution is reduced to that figure. On the following day repeat the injection and make the third and fourth injection if indicated by a rise of the temperature. If the injections of chemical are too many days apart, with a subsequent return of fever, the empyema may persist as it has done in 2 cases that we watched. These are the only ones where the empyema did not end in the course of a week or 10 days. The injections must be made frequently during the first week. We have noted that in the pus, removed after the chemical has been injected, the pneumococci can be seen in the smears and will show the "quellung" phenomenon but they will not grow when transplanted to media. The pus is therefore sterile. This observation we have frequently noted. It is not at all likely that all empyema will respond favorably and under such conditions the empyema must be treated in the usual surgical way. As yet we have not met this exception, but our cases are relatively few in number. We have had one experience with an interlobar empyema which was very difficult to reach with the needle. Cases of this type may always be hard ones to solve, but if one can reach the pus it is possible to treat it by the chemical method of injection. Empyema is not a serious life-endangering problem in the adult, providing it is recognized, but in childhood it is a much more serious affair. As we referred to previously, all the literature that we have been able to locate pertained to the empyema of children, and the results were, according to the authors,

very good. The child's empyema problem may therefore be a favorable field for reinvestigation as also the whole question of pneumonia in young children, which next year is to be studied at the Children's Hospital in Pittsburgh.

Conclusions. 1. Hydroxyethylapocupreine has not produced any visual disturbance in 200 patients who were given large doses of the drug.

2. There has been, especially during the past year, a lowering of the expected mortality. In the positive blood culture group there were 19 recoveries, or 59% mortality, whereas in the non-treated series there were only 4 recoveries, or 85% mortality.

3. The treatment of pneumococcic empyema by the closed method with injections of a 1 or 2% solution of hydroxyethylapocupreine has been effective in a small series of cases.

4. Mixed infection (*H. influenzæ* and *Strep. hæmolyticus*) has been present to a marked degree during the winter and spring of 1937 in our community.

The authors wish to express their thanks for the assistance during the past year to Drs. M. M. Bracken and George E. Crum. Further studies on the experimental side of this problem will be published.

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THE TREATMENT OF ACUTE INFECTIOUS ARTHRITIS OF UNDETERMINED ORIGIN WITH ARTIFICIAL FEVER.*

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The satisfactory results observed from the treatment of acute gonorrheal arthritis with artificial fever therapy have been fre-

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quently described. Hench *et al.*,[5] reviewed the reports which appeared since 1932. The results showed cures in from 50 to 100% of the patients treated, with relief in an average of 92%. Other series in which similarly good results were obtained have subsequently been reported by Schnabel *et al.*,[10] Kendell *et al.*,[6] and Stecher *et al.*[11] Little or no attention has been devoted to the efficacy of fever treatment in acute non-specific infectious arthritis and it seems desirable, therefore, to report the results obtained in the following series.

This condition has received scant attention in the literature, though its existence is strongly implied by several authors. Pemberton[9] does not mention it. Cecil[2] has no place for it in his classification of arthritis. In discussing the diagnosis of rheumatic fever, however, he says it must be differentiated from "Infectious arthritis, particularly in the subacute or febrile form. . . . In both conditions there is migratory swelling with pain in the joints, and when infectious arthritis is accompanied by fever, the clinical picture presented by these two infections is quite similar. . . . The history of previous attacks will not always settle the question, as the patient may have several attacks of infectious arthritis. However, repeated attacks of infectious arthritis usually will leave some slight deformity, especially in the fingers." Hench[4] describes many different specific types of acute infectious arthritis, but makes no provision for a similar disease of unknown etiology. Under differential diagnosis, however, he refers several times to "acute infectious (atrophic) arthritis." Such neglect of the subject in the literature is surprising because the disease has been more frequently encountered in this clinic than most of the types described by Hench and Cecil.

As a clinical entity, acute infectious arthritis is characterized by an acute onset of migratory arthritis associated with moderate fever, leukocytosis and rapid sedimentation rate. It is distinguished from gonorrheal arthritis, which it may simulate closely in all other respects, by a negative history and a lack of objective evidence of gonorrhea. Acute infectious arthritis differs from acute rheumatic fever in that it involves one or two joints following the brief migratory onset. Evidence of joint destruction is common. Effusions which have been examined contained neutrophils but were never grossly purulent, while smears and cultures revealed no organisms. In this respect the disease suggests atrophic arthritis. In fact, acute infectious arthritis ultimately may become chronic and assume all the characteristics of atrophic or rheumatoid arthritis.

It is difficult and in some cases impossible at the onset to distinguish between gonorrheal arthritis, acute rheumatic fever and acute non-specific infectious arthritis. All three may manifest fever and leukocytosis and exhibit migratory involvement of numerous joints with pain, tenderness, heat, swelling and effusion. Prompt

subsidence of symptoms with salicylate therapy, the absence of joint damage and the appearance of cardiac murmurs support the diagnosis of rheumatic fever. Evidence of active gonorrheal infection, or a recent history of gonorrhea closely associated in point of time with the appearance of joint symptoms, strongly suggest the diagnosis of gonorrheal arthritis which is, however, never proved until the organisms are recovered from the joint.

The material presented in this paper consists of 20 cases of acute non-specific infectious arthritis. All patients here considered had an unsatisfactory response to salicylate therapy and none developed cardiac murmurs during the period of observation. Only one patient (S. W.) had a previous history of arthritis, an acute attack 3 years before which had produced definite joint changes in an ankle. Six patients developed roentgenographic evidence of joint damage during the present illness. No evidence of gonorrheal infection was discovered. All patients had negative prostatic or cervical smears. Several gave histories of previous gonorrheal infections but none had occurred during the preceding 3 years. The diagnosis of acute rheumatic fever and gonorrheal arthritis seemed to be satisfactorily excluded in these patients.

All but 2 of the patients were in hospital for at least part of their treatments and all have been seen subsequently in the dispensary. In addition to fever therapy they were treated with bed rest and acetylsalicylic acid as indicated. Two patients (A. B. and W. T.) required traction for correction of flexion deformities after the acute symptoms of arthritis had subsided and one (R. B.) had traction followed by a hip spica. One patient (R. S.) required capsulotomy; one (L. C.) had a tonsillectomy; one (E. D.) had aspiration of a knee before fever therapy was instituted; one (D. S.) received 4 injections of typhoid vaccine with good febrile response after cabinet fever therapy had been discontinued.

Apparatus and Procedure. All fever treatments were given with the Kettering Hypertherm, which usually produced a rectal temperature of 105° F. in about an hour. The breeze from an electric fan was directed toward the patient's head, and ice rubbed on his face for comfort. Sodium amytal and morphine were given for sedation, and iced saline to relieve thirst and to replace chlorides lost by sweating. A nurse was in constant attendance. Temperatures of 105° F. to 106° F. were usually employed and were maintained about 5 hours. Occasionally lower temperatures were used and were continued for shorter periods when it seemed advisable to terminate treatments prematurely. Descriptions of the apparatus and procedures [5,6,10,11] in greater detail have been described repeatedly, particularly in relation to the treatment of gonorrhea.

Results. The most important data are presented in 2 tables, with cases listed in order of increasing duration of arthritic symptoms. The number of fever treatments may be estimated by considering that each treatment lasts from 3 to 5 hours. The actual time spent in the cabinet is much longer, since the period (about

1 hour) required for the temperature rise is not included. Treatments are listed as "hours above 105° F.," although at times the temperature would drop below this level for short periods. In most cases it was maintained continuously above 105° F.

Table 1 shows the data on 12 patients who received complete relief or cure of all joint symptoms. This means that they were free of pain and tenderness; the joints were normal in appearance and were able to perform satisfactorily all the motions required by the patient's usual activity without attracting the attention of an observer. One patient (A. K.) showed incomplete extension and slight enlargement of the metacarpophalangeal joint of a fore-

TABLE 1.—ACUTE NON-SPECIFIC INFECTIOUS ARTHRITIS WITH COMPLETE RECOVERY.

	Sex.	Age.	Duration of arthritis (in weeks)	White blood count on admission.	Sedimentation rate.*	Type of onset.	Major involvement.	Roentgen ray.	Fever hours of 105° F	Comment.
M. B.	F.	21	1	11,100	80	Migratory	Finger	Neg.	8	
J. K	M.	42	1	10,300	106	....	Knee, ankle	None	2	
E. D.	M.	48	2	15,000	84	....	Knee	Neg.	5	Onset with chills. Knee was aspirated.
G. S.	M.	51	2	7,500	108	Migratory	Hands	See note	3	Hypertrophic arthritis of ankle by Roentgen ray.
D. S.	M.	24	2	8,300	110	....	Knee	Neg.	10	
E. W.	M.	29	2	20,000	90	Migratory	Knee	None	5	Iritis.
E. F.	M.	47	3	9,600	35	....	Ankle, wrist	Neg.	6	
A. K.	F.	24	3	7,500	127	Migratory	Hand	Erosion	8	Onset after delivery.
C. H.	M.	34	4	12,100	60	Migratory	Hand, elbow	None	6	
F. K.	M.	48	6	16,000	100	Migratory	Wrist, elbow	None	6	
D. S.	F.	39	8	14,000	100	Migratoy	Wrist, elbow	None	4	Had 4 injections T. A. B.
J. F.	M.	32	10	9,400	102	Migratory	Wrist, knee	None	25	

* Sedimentation rate by a modified Westergren method. Oxalated but undiluted blood was set up in tubes graduated to 200 mm. and read at the end of 1 hour without correction for anemia. A reading of 20 mm. or less is regarded as normal.

finger 3 months after treatment. This was the only joint involved. A Roentgen ray photograph before treatment showed slight erosion at the edge of the joint, and 3 months later a subsequent film showed mild hypertrophic changes throughout the joint. Roentgen ray photographs were made of the affected joints of 5 other patients of this group. All were normal save one (G. S.), which revealed hypertrophic changes, interpreted as having no significant relationship to the acute infectious arthritis.

Table 2 includes the data on 8 patients who received partial relief. Three of these patients (L. C., S. C., and L. A.) were free of all signs of joint disease after one or two treatments. They had no swelling, tenderness or limitation of motion but they did complain of vague aches and pains which caused them to return to the

dispensary for further relief. Roentgen ray photographs of the affected joints were negative. One patient (S. W.) had a similar result except that the Roentgen ray picture showed erosion at the edge of a metacarpophalangeal joint of a middle finger. A later picture showed mild hypertrophic changes, and he then had incomplete extension. The patient was able to work as a railroad brakeman.

Roentgen ray studies of the affected joints were made on all the patients of this group. In 3 patients (L. C., S. C., and L. A.) these were entirely negative. In 2 cases with joint damage (W. T. and A. B.) one treatment relieved pain and tenderness but marked

TABLE 2.—ACUTE NON-SPECIFIC INFECTIOUS ARTHRITIS WITH PARTIAL RELIEF.

	Sex.	Age.	Duration of arthritis (in weeks)	White blood count on admission.	Sedimentation rate.*	Type of onset.	Major involvement.	Roentgen ray.	Fever hours of 105°F	Comment.
L. C.	F.	21	2	8,000	115	Migratory	Knees, wrists	Neg.	30	Migratory symptoms without signs for 3 months.
S. W.	M.	30	4	12,000	25	....	Hand	Erosion	20	Migratory symptoms; works as brakeman.
R. B.	F.	14	4	11,800	137	Migratory	Hip	Erosion	12	Lost all motion after using a spica.
S. C.	M.	40	5	13,000	114	Migratory	Knees, wrists	Neg.	22	Migratory symptoms after treatment.
W. T.	M.	40	5	9,150	60	....	Knee	Erosion	15	Required traction for flexion deformity.
A. B.	F.	43	7	8,100	130	Migratory	Knee	Erosion	5	One treatment relieved pain. Required traction for flexion deformity.
R. S.	F.	26	11	7,600	85	Migratory	Knee	Erosion	25	Required capsulotomy.
L. A.	F.	24	16	18,000	113	Migratory	Hands, knees	Neg.	6	Migratory symptoms without signs for 2 months.

* Sedimentation rate by a modified Westergren method. Oxalated but undiluted blood was set up in tubes graduated to 200 mm. and read at the end of 1 hour without correction for anemia. A reading of 20 mm. or less is regarded as normal.

flexion deformity remained. Two subsequent treatments were given to one (W. T.) without improvement of the deformity. Traction in both cases produced correction and the patients have satisfactory joints with painless motion from complete extension to 90 degree flexion. One patient (R. S.) noted substantial but not complete relief of pain and tenderness. Her flexion deformity could not be corrected by traction or casts and a capsulotomy was eventually performed. The remaining patient in this group (R. B.), entered the hospital with a history of severe migratory arthritis of 3 weeks' duration. Examination revealed that all joints had subsided except the right hip which was extremely painful and was held motionless in flexion, abduction and external rotation. Her temperature was high, heart rate rapid, and there was leukocytosis. The provisional diagnosis of rheumatic fever was abandoned after salicylate therapy proved ineffective, and a Roentgen ray picture revealed marked demineralization with destruction of the head of the femur and the upper portion of the acetabulum, suggesting

gonorrheal or tuberculous arthritis. Further study indicated that neither of these infections was present. The first treatment caused definite diminution of pain and reduction of the fever. Two more treatments brought the temperature to normal, eliminated tenderness and relieved spontaneous pain. Traction then corrected the deformity, and the muscle spasm subsided. Motion of the hip at this time was painless and limited from full extension to 60 degrees of flexion with about 30 degrees of internal rotation. Abduction and adduction were slight. Because of marked demineralization of the head of the femur and the acetabulum unprotected weight bearing seemed hazardous and likely to cause deformity of the joint structures. For this reason a walking hip spica was applied before the patient went home. On removal of the spica 6 weeks later the hip was found to be motionless. This lack of motion seemed to be due to hypertrophic changes and bone proliferation about the rim of the acetabulum. The joint space had nearly disappeared but the line of separation between the bones was distinct and there was no evidence of true bony ankylosis.

Two similar cases which occurred in our series of gonorrheal arthritis were given bed exercises for 1 and 2 months until remineralization had taken place and both now have painless movable hips.

Comment. Not only did 60% of the 20 patients make complete, prompt recovery and 40% have partial relief, but the duration of the disease was shortened in all, its severity decreased, the incidence of joint damage lessened and the joint damage which did occur minimized by artificial fever therapy. These results compare favorably with those which have been reported in cases of gonorrheal arthritis treated with fever therapy.

The tables reveal that the 12 patients receiving complete relief had arthritis symptoms from 1 to 10 weeks (average 3.6 weeks), before fever therapy was instituted. These patients received from 2 to 25 hours of fever (105° F.) for relief (average 7.3 hours). The 8 patients having only partial relief had arthritic symptoms from 2 to 16 weeks before fever therapy was instituted (average 6.7 weeks). This group received from 5 to 30 hours of fever (average 17 hours). It is noteworthy also that 5 of the 6 patients showing Roentgen ray evidence of joint damage were of the group of longer duration. These findings indicate the importance of prompt therapy in an effort to avoid or minimize the joint damage. The satisfactory results observed in the first group were obtained with relatively small amounts of fever. Despite the fact that the patients receiving only partial relief had nearly twice as much fever as those in the first group, the authors now feel that several patients suffered from inadequate fever. This is particularly true of one patient (R. B.) who had 3 treatments of 4 hours' duration at weekly intervals. She was treated soon after we started using fever therapy: a period

when conservatism was indicated by inexperience. In an acute disease of short duration there appears to be no reason to delay the second or third treatment more than 3 or 4 days.

The complications of fever therapy encountered in this series were neither as frequent nor as severe as those seen in our series of gonorrheal arthritis.[11] Because the degree of fever desired and attained was more moderate, 105° F. in this series as compared with 107° F. or higher in the other, the air temperature of the cabinet was maintained at a consistently lower level, discomfort of the patient was less severe, and delirium was rare, while coma, collapse and uncontrolled hyperpyrexia were not seen. Sedation was less difficult, and smaller doses of sodium amytal and morphine were necessary than in treating gonorrhea. Consequently, delirium from sodium amytal and nausea from morphine, which proved a troublesome problem in many patients treated at higher temperatures, rarely occurred in this series, and severe erythemata and skin burns usually were avoided. One treatment was terminated after 4 hours because of blisters. This patient (D. S.) subsequently developed second degree burns which made further fever treatment inadvisable at the time. One complication, the occurrence of herpes labialis, developed as frequently in the present series as it did in the series treated at the higher temperature. About one-third of the patients in each series developed herpes labialis but it occurred only after the first treatment.

Discussion. Although the treatment of acute infectious arthritis with artificial fever must be regarded as empirical, its use is not without precedent. Protein shock therapy,[2,9] such as boiled milk injections or typhoid vaccine intravenously, has been used with some success in various types of arthritis for years and still enjoys popularity. Similar therapy for chorea and rheumatic fever[12] is highly recommended, and the authors of recent reports[8] are enthusiastic in praise of mechanical fever for chorea. The causes of acute rheumatic fever, chorea and atrophic arthritis have not thus far been indisputably demonstrated, but there is much evidence to indicate that streptococci are concerned in all three, together with other factors not clearly understood.

There has been no adequate explanation for the beneficial effects of fever therapy in acute infectious arthritis. The mechanism is not clear. In such a disease of unknown etiology there is no justification for assuming that high temperatures directly produce death or destruction by thermal injury to the causative agent. In only two diseases, gonorrhea[1] and syphilis,[3] has it been established that this may occur. Patients with these diseases can tolerate temperatures of sufficient height and duration to sterilize *in vitro* cultures of the causative organisms. Thermal death time studies of cultures of many other pathogenic organisms show them to be more tolerant

of high temperatures than is man.[7] The streptococci are among this group of more thermostable organisms.

Definite physiological changes are produced by artificial fever.[5] The blood flow, circulatory rate, cardiac output and metabolism are increased. An increase in the number and size of capillaries has been observed to occur in the nail bed, and the drop in diastolic blood pressure and the rise in the pulse pressure indicates that this change is general throughout the body. The leukocyte count, after an initial fall, shows a substantial rise and the rate of phagocytosis increases. Reports on agglutinins, complement and opsonic index are variable. It seems probable that the beneficial effects of artificial fever depend upon factors which are not entirely recognized.

Summary. Acute non-specific* infectious arthritis is a relatively common syndrome which may be differentiated from acute rheumatic fever and acute gonorrheal arthritis by certain well defined distinguishing characteristics. It has received scant attention in the literature and may be regarded as an acute form of atrophic, rheumatoid or chronic infectious arthritis. Of the 20 cases of acute non-specific infectious arthritis treated with artificial fever therapy, 12 (60%) received prompt relief and apparent cure, while 8 (40%) were partially relieved. The course of the disease was favorably modified in every case. These results compare favorably with those observed in the treatment of acute gonorrheal arthritis by artificial fever.

Treatment consisted of induced fever (about 105° F.) by means of the Kettering Hypertherm, maintained usually from 4 to 5 hours. The patients who recovered completely received from 2 to 25 hours of fever (average 7.33 hours). The patients with partial relief received 5 to 30 hours of fever (average 17 hours).

The use of artificial fever in this condition is empirical but not without precedent. The mechanism producing benefit is not understood.

* By non-specific is meant a process that is obviously infectious and yet has not had the causative organism or organisms identified.

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EXPERIMENTAL STUDIES ON THE EFFECT OF TEMPORARY OCCLUSION OF CORONARY ARTERIES IN PRODUCING PERSISTENT ELECTROCARDIOGRAPHIC CHANGES.*

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According to current belief, both angina pectoris and cardiac infarction are the result of myocardial ischemia. In each the underlying mechanism seems to be a relative disproportion between the requirements of the heart for blood and the supply furnished by the coronary arteries; the changes resulting from this situation depend solely upon the extent and duration of the relative ischemia of the myocardium, however it may be produced. Thus, the syndrome of Heberden's angina pectoris is due to temporary ischemia, while the manifestations of coronary occlusion are the result of a permanent ischemia, with infarction of the muscle supplied by the occluded vessels. In patients with clinical evidence of coronary occlusion, infarcted areas of the cardiac musculature are not infrequently disclosed at postmortem examinations even though the arteries supplying the area, while they may be narrowed, are not completely occluded. Similarly, many patients with angina pectoris show persistent electrocardiographic abnormalities during life, and at postmortem examinations present small areas of cardiac fibrosis despite the absence of occluded arteries. It would thus appear that temporary ischemia may result in certain irreversible electrocardiographic and anatomic changes. The situation is analogous to that occurring in carbon monoxide poisoning where, despite restitution of normal blood oxygen, severe neurologic disturbances occur because the temporary ischemia has been sufficient to produce irreversible changes in the brain which lead to necrosis.

In an experimental investigation of the reaction of the myocardium to temporary ischemia, the following manifestations of deficient myocardial nutrition may be considered: 1, Disturbances of the

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myocardial metabolism; 2, changes in cardiac rhythmicity and contractility; 3, alterations in the ventricular electrocardiographic complexes; 4, necrosis of myocardial fibers.

These changes and their degree indicate the existence of impaired myocardial nutrition and serve as an index of its severity. In man, they are reflected in the signs and symptoms of coronary disease.

The Arrhythmias of Cardiac Ischemia. Erichsen,[8] in 1842, reported "tremulation of the ventricles" within 30 seconds to 2 minutes following ligation near the origin of main coronary arteries in rabbits and in dogs. Subsequently, many other investigators observed slowing, irregularities of rhythm, and finally ventricular fibrillation after sudden occlusion of one or more main coronary trunks in rabbits, dogs and cats.[1a,b,3,6,7,13,16–18,23,26,31] In many instances the appearance of ventricular fibrillation was observed within a few seconds after occlusion, while at other times ligation of the same artery resulted either in no fibrillation or in fibrillation some hours after occlusion. Sudden release of the ligature occluding a main artery or one of its branches has been observed to initiate extrasystoles and ventricular fibrillation within a few seconds.[7,10]

Ligation of lesser branches of the main coronary arteries produced ventricular fibrillation much less frequently. Continuance of normal auricular contraction despite the arrhythmia of the ventricles has been described.[26]

From these and other reports it appears that the following factors may exert an important influence in precipitating ventricular fibrillation: 1, size of artery occluded; 2, region of heart supplied by the artery occluded;[12] 3, duration of occlusion; 4, nature of the anesthesia;[14] 5, activity of autonomic nervous system;[13b,27] 6, changes consequent to reëstablishment of circulation.

The Dynamics of the Heart in Coronary Occlusion. The decreased force of myocardial contraction consequent to coronary ligation was observed by Erichsen,[8] von Bezold[1a,b] and other early experimentors, and has been recognized by all subsequent workers. It remained, however, for Tennant and Wiggers[28] to devise a method for optical registration of the contraction of portions of myocardium *in situ*, and to show that the force of contraction fails within a minute after occlusion of the coronary artery supplying the region studied. They found that when circulation was reëstablished after 20 minutes or less the myocardial contractility returned to normal, while with longer occlusion recovery did not take place. Their experiments were, however, acute and it is not known whether recovery might have occurred several hours or days later.

The Electrocardiogram in Coronary Occlusion. Changes in the electrical behavior of heart muscle following coronary occlusion were first described by Samuelson in 1880.[25] Using the rheoscopic frog preparation as an index of electrical activity in the heart, he found that when a coronary artery was occluded in a curarized

rabbit, the frog muscle ceased to contract as soon as the effects of the occlusion could clearly be recognized by change in color of the ventricle and alterations in rhythm. Within ½ to 1½ minutes after release of the ligature, contractions of the rheoscopic preparation returned to normal. This experiment could be repeated many times in the same animal with the identical results. It has since been recognized that characteristic alterations of the ventricular electrocardiogram may develop very shortly after coronary occlusion, both in man and in experimental animals. Otto,[21] Parade,[22] Wood and Wolferth,[31b] Wilson, Hill and Johnston,[30] Garcia del Rio and Orias,[9] and others have detected these changes within 1 to 10 minutes after experimental coronary occlusion. Several of these authors[11,31a] have also shown, as did Samuelson, that if the circulation is reëstablished after but 1 to 3 minutes of occlusion, the electrical activity of the ventricles returns promptly to normal. Determinations have not been made of the time of occlusion necessary to produce permanent or long lasting electrocardiographic changes.

Myocardial Necrosis. It has long been recognized that infarcts in the myocardium may result from occlusion of coronary arteries, and the investigations of Büchner[4a,b,c] and others[5,19] have demonstrated that prolonged cardiac anoxemia from other causes may also cause necrosis. Temporary occlusion for 2 hours or more, when followed by reëstablishment of circulation, has been found to lead to necrosis of the myocardium supplied by the occluded vessel, while occlusion for 30 minutes was not followed by necrosis.[10,24,29]

It is evident from this survey of available knowledge that adequate data are lacking concerning the following questions:

1. May temporary interruption of the blood supply to a part of the heart produce persistent electrocardiographic changes?
2. If this proves to be the case, how long must such temporary ischemia be maintained in order to produce persistent electrocardiographic changes?
3. What is the relation between the duration of coronary circulatory arrest causing electrocardiographic changes and the duration of arrest required to produce myocardial necrosis?
4. What effect has the duration of temporary circulatory arrest upon the development of cardiac irregularities during the arrest and after reëstablishment of a normal blood supply?

The present studies were designed to gain evidence in regard to these considerations.

Methods. In 24 cats the anterior descending branch of the left coronary artery or one of its larger ramifications was occluded for varying lengths of time.

With the animal under ether anesthesia and artificial respiration, the heart was exposed through an intercostal approach. The pericardium was opened; the artery to be occluded was dissected free from the adjacent tissue over a length sufficient to allow a silk or catgut ligature to be placed

loosely beneath it. The accompanying vein was never included in the ligature. At the appropriate time gentle traction was exerted on the ligature to the point of complete occlusion of the artery, and subsequently released after periods of traction varying from 5 to 40 minutes. The ligature was then removed, the pericardium sutured, and the chest closed. Fifty cc. of 5% glucose in physiologic saline was given intraperitoneally and the animal placed in a warm room.

Electrocardiographic tracings from Leads 1, 2 and 3 were taken with the ligature in place just before traction was begun. In each animal a continuous tracing was taken from Lead 2, starting just before traction was exerted, and running for approximately 1 minute after the beginning of traction. Records were taken from Lead 2 or all three leads at intervals of 2 to 10 minutes during traction. Lead 2 tracing was again started just before release of traction and continued until approximately 1 minute after release. Electrocardiographic tracings from all three leads were repeated at intervals, up to 30 minutes after release of traction, and at 1 to 2-day intervals until the animal was sacrificed.

The cardiac musculature was observed carefully for changes in contraction and color before, during and immediately after traction. Inspection of the freed coronary vessel distal to the point of traction demonstrated its complete obstruction during traction, and the reëstablishment of blood flow upon release. The animals were sacrificed 6 to 9 days after operation. At this time the heart was again exposed under ether anesthesia and artificial respiration, and observations were made of the appearance of the myocardium and of the vessel which had been temporarily occluded; the patency of this vessel was demonstrated by observation of bleeding after incision below the point of previous ligation.

The heart was then removed, examined for gross changes in the myocardium, and fixed in 5% solution of formaldehyde. Cross sections of the heart were made at various levels above and below the point of occlusion and were studied to determine changes in the myocardium and in the coronary vessels. Sections of the coronary artery at the region of the tie demonstrated the absence of traumatic changes or thrombus formation.

Control observations were made on 6 cats. In 4, the ligature was put in place and then removed without occluding the vessel; the animals were allowed to survive and electrocardiographic tracings were made in 3 on the day after operation; in the fourth, at intervals during the week following operation. At the time of sacrifice, anatomical studies of the heart were made in each animal. In the other 2 control experiments the ligature was permanently tied; electrocardiographic tracings were obtained at intervals during the postoperative week and anatomical studies were made.

Results. A. *Electrocardiographic Changes.* Electrocardiographic changes following temporary coronary artery occlusion are summarized in Table 1. In all but 2 of the cats studied, tracings showed the development of definite anoxemic changes within 1 minute after traction was applied; in the other 2 cats definite changes were first evidenced at 2 and 15 minutes after the beginning of traction. These changes became more pronounced during the time of occlusion, and, while they generally persisted immediately after release of the ligature, they were somewhat less pronounced (Table 1). They consisted in definite alteration in the *R* or *S-T* take-off elevated or depressed *S-T* segments and marked changes in the *T* waves (Figs. 1, 2 and 3). Changes in the direction of the *QRS* complexes were occasionally witnessed, but evidences of intraventricular block were not seen.

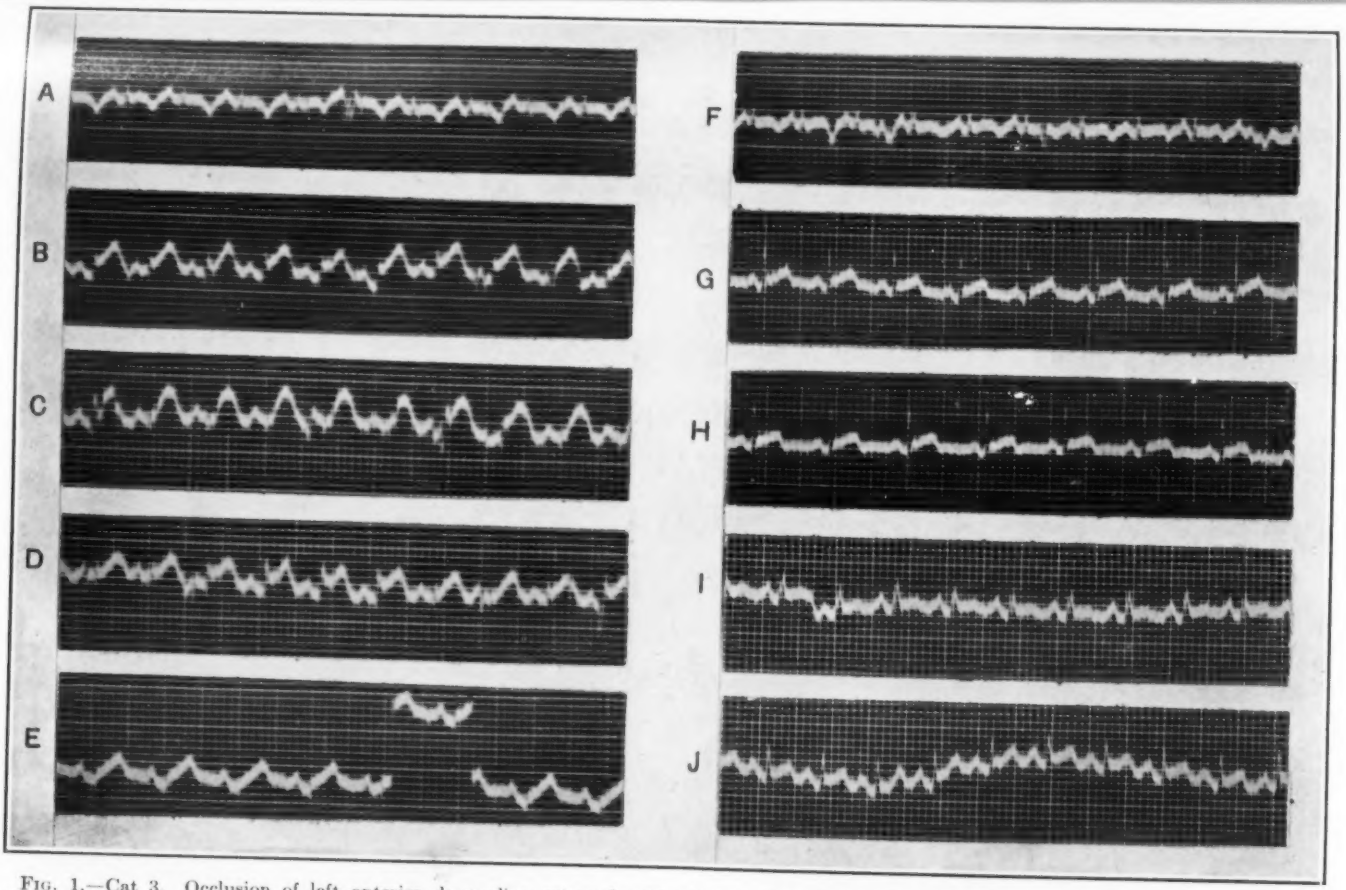

FIG. 1.—Cat 3. Occlusion of left anterior descending artery for 10 minutes. Lead 2 throughout. *A*, Control; immediately before traction; *B*, after 1 minute of traction; *C*, after 4 minutes; *D*, after 10 minutes; immediately before release; *E*, 11 minutes (1 minute after release); *F*, first postoperative day; *G*, second postoperative day; *H*, sixth postoperative day; *I*, seventh postoperative day; *J*, eighth postoperative day.

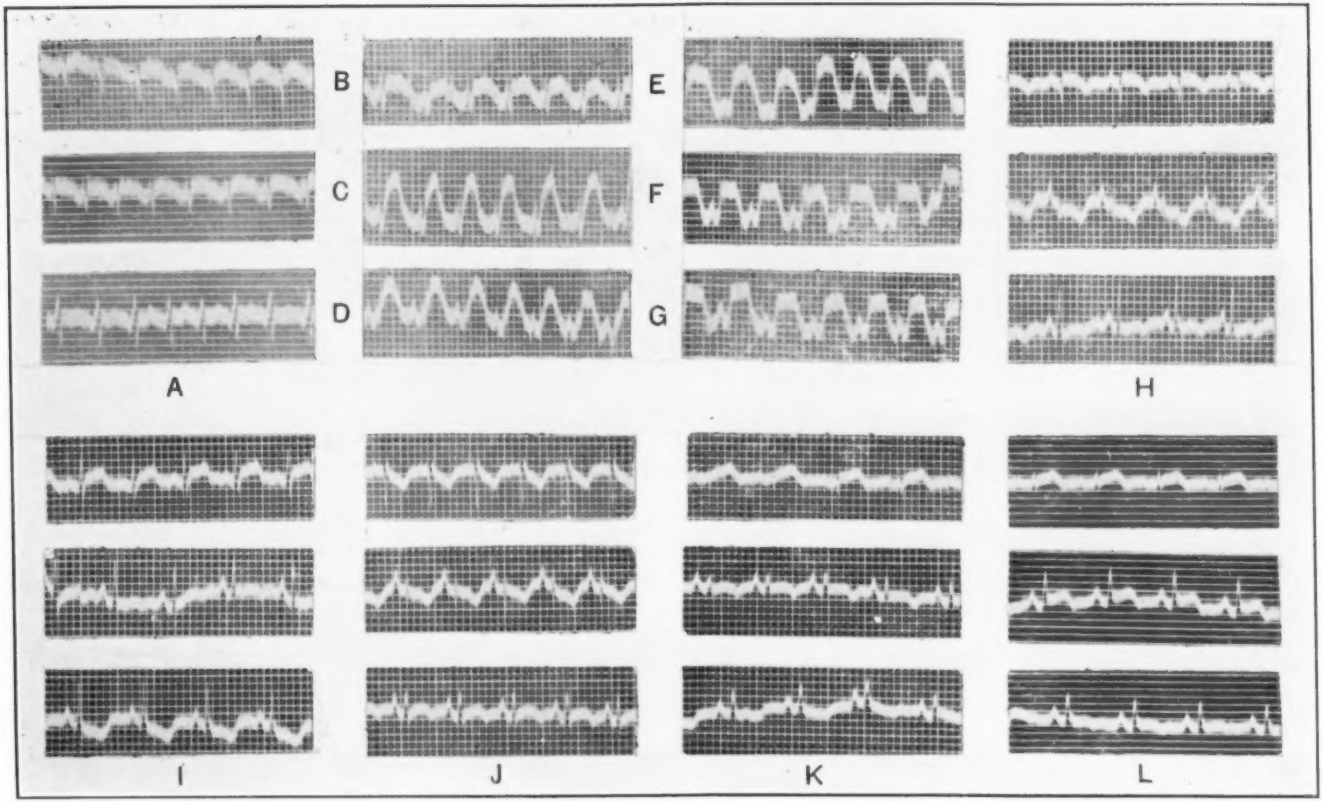

FIG. 2.—Cat 3. Occlusion of left anterior descending artery for 10 minutes. Electrocardiograms by the conventional three leads were of the interior infarction type. *A*, Control (three leads); *B*, 10 seconds after traction (Lead 2); *C*, 20 seconds (Lead 2); *D*, 1 minute (Lead 2); *E*, 8 minutes (Lead 2); *F*, 9 minutes (Lead 2); *G*, 10 minutes (Lead 2); *H*, three leads in this and following columns; first post-operative day; *I*, third postoperative day; *J*, fourth postoperative day; *K*, sixth postoperative day; *L*, seventh postoperative day.

These electrocardiographic changes persisted during the entire postoperative period in all cats in which the period of occlusion was 15 minutes or longer. Persistent electrocardiographic changes were observed, however, in only 3 of the 6 experiments in which traction was exerted for 10 minutes or less. One of these 3 animals showed changes until sacrificed 8 days postoperatively. The changes during

TABLE 1.—ELECTROCARDIOGRAPHIC CHANGES FOLLOWING TEMPORARY CORONARY ARTERY OCCLUSION IN CATS.

Cat No.	Date (1936).	Duration of occlusion (min.).	Degree of electrocardiographic abnormalities.		Postoperative electrocardiographic abnormalities.		Sacrifice of animal, days post-operative.
			During occlusion.	Immediately after occlusion.	Duration (days).	Degree.	
1	6/3	5	++	....	2	+++	8
2	5/27	6	+	....	0	0	7
3	6/3	10	+++	+	8	++	8
4	4/24	10*	+++	V.F.	0	0	6
5	5/25	10	++	+	0	0	9
6	4/17	10	+++	+	3	+	7
7	4/22	15	....	....	7	++	7
8	4/17	15	....	....	7	+++	7
9	4/24	15	+++	++	6	+++	6
10	5/18	20	+++	++	....	....	1§
11	5/10	20	+++	++	7	++	7
12	5/13	20	+	+	6	+	6
13	4/21	20	+	....	7	+	7
14	4/22	20	+++	0	2	+	2§
15	5/11	25	+++	+	1	++	1§
16	5/8	30	+++	0	7	++	7
17	5/8	30	+++	+	7	+++	7
18	5/8	30	+++	+	3‖	++	8§
19	5/13	30	+	+	6	+	6
20	5/11	35	+++	++	7	++	7
21	5/11	40*	+++	V.F.	....	....	1§
22	6/3	3†	++	V.F.	....	....	0§
23	5/8	30‡	++	V.F.	....	....	0§
24	5/13	30‡	....	V.F.	....	....	0§

* Fibrillated on release of ligature. Recovery.
† Fibrillated during occlusion. Death.
‡ Fibrillated on release of ligature. Death.
V.F. = Ventricular fibrillation.
‖ Last electrocardiograph taken.
§ Animal died.

the postoperative period varied somewhat from day to day, but generally were qualitatively similar to those witnessed during occlusion. In almost all instances the electrocardiographic changes were those characteristic of anterior infarction and corresponded closely to the deviations produced by permanent ligature of the same artery in two controls.

In 3 of the 4 experiments in which the ligature was put in place

and then withdrawn without traction, electrocardiographic records taken before and after the procedure were practically identical. In the fourth experiment, minimal changes were noticed in Lead 2

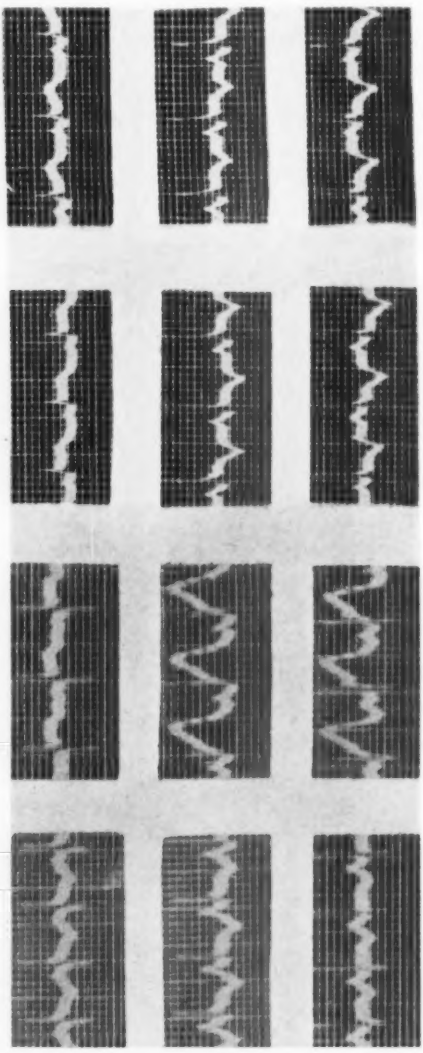

FIG. 3.—Cat 9. Occlusion of left anterior descending artery for 15 minutes, showing electrocardiograms of conventional three leads just before occlusion of the artery, 5 minutes after the beginning of occlusion, and 1 and 5 days after the operation.

but were insignificant in comparison to the results following temporary occlusion. These findings, together with the absence of electrocardiographic changes postoperatively in 3 of the 6 animals

in which occlusion was maintained for 10 minutes or less, constitute important evidence that other factors such as pericarditis or local thrombosis were not significant in producing the electrocardiographic changes observed in this study.

B. *Changes in the Myocardium.* Within a few seconds after application of traction on the artery, the myocardial area supplied became cyanotic and showed diminished contraction. These changes became more pronounced during the period of traction; when the ligature was released the affected portion of the myocardium resumed its normal color.

On sacrificing the animals no gross or histologic evidences could be found which might be interpreted as due to the temporary occlusion. Minute areas of focal necrosis were found histologically, but similar areas were also seen in unaffected areas of these hearts and in the hearts of a large series of normal cats. Permanent ligation of the same arteries in 2 control cats resulted in definite infarcts.

C. *Arrhythmias.* Soon after the onset of traction isolated ventricular extrasystoles were frequently encountered, which, with but one exception, did not proceed to paroxysmal ventricular tachycardia or to ventricular fibrillation during occlusion. Shortly after release of traction, however, 4 of the 24 animals rapidly developed ventricular fibrillation, from which 2 died.

Discussion. In the light of these findings it appears that temporary cardiac ischemia may result in lasting electrocardiographic changes, in the absence of any discernible histologic evidence of myocardial necrosis. In all of the 13 animals in which occlusion of the anterior descending branch of the left coronary artery or one of its main branches was for 15 minutes or longer, significant deviations from normal persisted postoperatively until the animal was sacrificed on the sixth to ninth postoperative days. The changes consisted in: 1, elevation or depression of the *S-T* take-off; 2, loss of the iso-electric *S-T* segment; and, 3, alteration in the direction, amplitude and contour of the *T* wave. These findings corresponded in every way with those following permanent occlusion of the same vessel in control experiments, and conform to those described as characteristic of infarction of regions of the anterior wall of the ventricles.

In all except 2 animals the first appearance of electrocardiographic changes was observed within 1 minute after occlusion of the vessel, and became more pronounced as occlusion continued. Immediately after release, these changes decreased somewhat in degree, and in 2 experiments an almost normal electrocardiogram was reëstablished. By the first postoperative day, however, these changes again became more pronounced, and then showed a tendency to gradual subsidence.

When occlusion was maintained for less than 15 minutes the changes in the electrocardiogram during the period of arrest of

coronary flow were as well pronounced as when the duration of occlusion was longer. In 3 of 6 such experiments, changes persisted for several days; in the others, significant alterations were not observed postoperatively. Of the 3 positive experiments, 2 showed changes only as long as the second and third postoperative days, while the other, in which the artery was occluded for 10 minutes, showed changes until sacrificed on the eighth day. No similar changes were found in 4 control experiments in which the entire operation was duplicated, with the sole exception of traction on the ligature.

Careful gross and microscopic examination of the hearts failed to reveal any areas of myocardial necrosis that could be attributed to the occlusion. They further demonstrated the absence of thrombi or other occlusion in the artery at the point of temporary occlusion or peripheral to it. The reëstablishment of normal blood supply following release of traction on the artery was verified by certain other observations: 1, following release of the ligature, the area supplied by the artery, which had been clearly demarcated by its cyanotic and edematous appearance, immediately resumed its normal color; 2, pulsation of the artery distal to the occlusion was immediately reëstablished and its lumen became filled with bright red blood; 3, at the time of sacrifice transection of the artery distal to the tie was followed by arterial spurts of blood. The absence of necrosis likewise indicates that permanent occlusion did not occur.

The unexpected production of long-lasting electrocardiographic changes without tissue necrosis raises interesting questions regarding the interpretation of the electrocardiogram in coronary disease. It is, of course, recognized that, experimentally, short periods of coronary insufficiency are followed by a rapid restoration of the altered electrocardiogram,[31a] while, on the contrary, sustained ischemia following permanent coronary artery ligation produces persistent electrical disturbances as well as anatomical lesions. It would seem that the observations recorded here fit into an intermediate zone between these two extremes, where myocardial damage has been just insufficient to cause gross tissue destruction, yet functional impairment was so profound that electrical recovery was not complete for periods as long as 9 days. It is not improbable that examination of the affected tissue by special techniques would reveal changes in its staining reactions and in its metabolism.

Counterparts of the conditions revealed in these experiments are seen in patients with angina pectoris. During attacks of angina pectoris, electrocardiograms characteristic of myocardial ischemia which revert to normal at the end of the seizure have been frequently obtained. Many patients with angina pectoris show peristent electrocardiographic abnormalities without postmortem evidence of coronary occlusion or myocardial infarction; the pathologic physiology that occurs in such cases appears to be similar to that of above experiments.

The circumstances under which ventricular fibrillation occurred in these experiments supports the view that this arrhythmia may occur in the absence of irreparable structural damage, for the duration of occlusion of these experiments was insufficient to produce signs of cardiac necrosis. The frequent occurrence of ventricular fibrillation in these experiments is in accord with the view that sudden death in angina pectoris is due to the onset of this arrhythmia. It is not surprising, therefore, that Levy and Bruenn[15] were unable to discover any pathologic explanation for the sudden death of several of the patients in their series.

It is significant that in practically every instance the onset of fibrillation occurred upon release of the ligature and reëstablishment of a normal blood supply to the damaged area. The development of ventricular extrasystoles soon after occlusion of the artery, although they did not proceed to ventricular fibrillation, and the frequent reports in the literature of rapid development of ventricular fibrillation soon after occlusion, suggests that the period of transition from normal to abnormal metabolism or *vice versa*, is the most favorable time for development of fibrillation. This view is emphasized by de Boer[2a,b] who pointed out that it is impossible for completely functionless myocardial tissue to give rise to ectopic rhythms. It is also in accord with the concept that ventricular fibrillation is not necessarily a manifestation of irreparable damage to the heart. This view is further supported by the observation that, clinically, ventricular fibrillation may occur in a variety of other circumstances: 1, the early stages of chloroform anesthesia; 2, acute benzol poisoning; 3, electric shock with low voltages; 4, following intravenous administration of adrenalin; 5, as a termination of paroxysmal ventricular tachycardia, in all of which conditions structural damage is not characteristically present. The occurrence of ventricular fibrillation in cardiac infarction and in other situations in which the heart is irreparably damaged may be due to the presence of zones of impaired nutrition in proximity to areas of complete ischemia.

Summary and Conclusions. 1. Since according to current belief angina pectoris and cardiac infarction are the result of myocardial ischemia, experiments were undertaken to learn whether temporary interruption of the blood supply to a portion of the heart would result in persistent electrocardiographic or anatomic changes.

2. Occlusion of the left anterior descending coronary artery or one of its branches for from 5 to 40 minutes with subsequent release of traction was performed in 24 cats. Twenty-one animals were allowed to survive for from 1 to 9 days after this procedure.

3. Electrocardiograms of the three conventional leads obtained before and at various intervals during and following occlusion revealed anoxemic changes persisting during the postoperative days in all animals in which occlusion was maintained for from 15 to 40 minutes inclusive. Only 3 of 6 animals in which the period of

occlusion was 10 minutes or less showed changes on the postoperative days; in one these changes persisted until sacrifice of the animal 8 days postoperatively. The electrocardiographic changes were characteristic of the anterior infarction type.

4. Postmortem examination failed to reveal gross or histologic evidences of cardiac infarction in any instance.

5. Cardiac irregularities consisting of ventricular extrasystoles and ventricular fibrillation were observed at times during occlusion but particularly on release of traction. Three of the 5 animals which developed ventricular fibrillation died immediately.

6. The clinical counterparts of these experimental observations are discussed.

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PULMONARY CIRCULATION IN ARTIFICIAL PNEUMOTHORAX AND ANTHRACOSILICOSIS.

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Postmortem examination[1] of 18 tuberculous lungs which had been collapsed under artificial pneumothorax for a period varying from 5 months to 3 years showed a marked shortening and narrowing

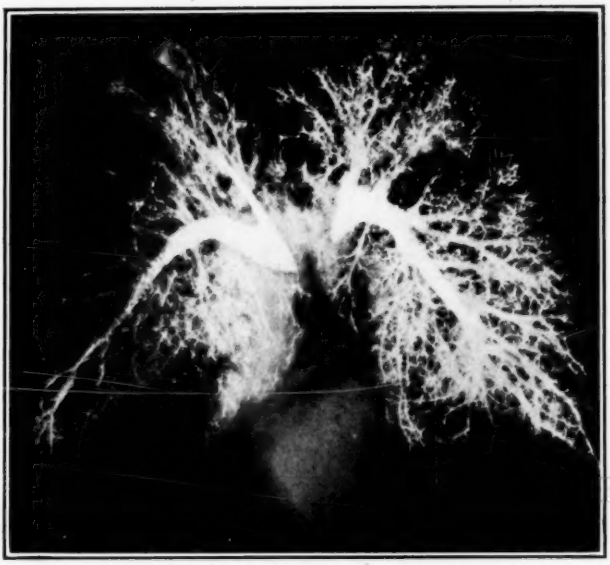

FIG. 1.—Case 6668, white female, aged 20, had pulmonary tuberculosis since August, 1935. The right lung was collapsed under artificial pneumothorax from June to November, 1936. Died in November, 1936. The right pulmonary artery and its branches are shorter and narrower than those in the left lung.

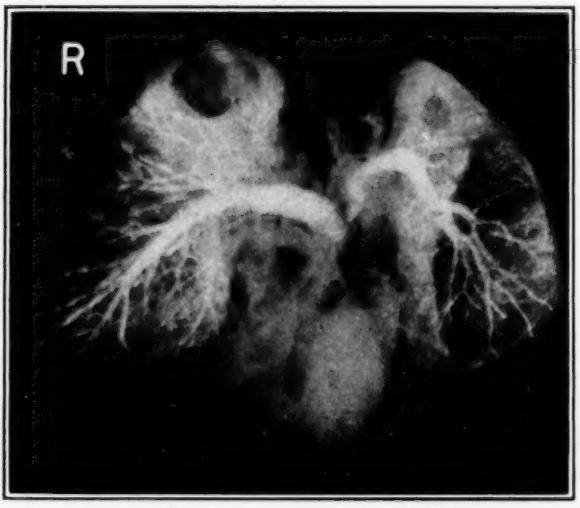

FIG. 2.—Case 6511, white female, aged 24, had pulmonary tuberculosis since January, 1933. The left lung was collapsed under artificial pneumothorax from August, 1934, to August, 1935. Phrenicectomy was done on the left in December, 1935. The left half of the diaphragm became elevated. Died in February, 1937. Note the marked narrowing and shortening of the pulmonary artery and its branches in the left lung.

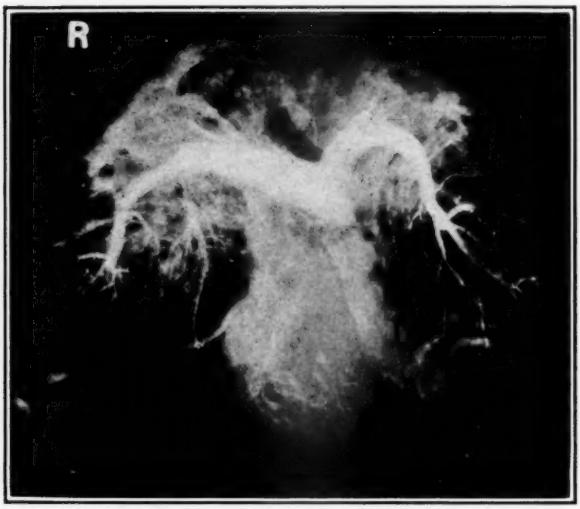

FIG. 3.—Case 9768, white male, aged 41, anthracite coal miner 16 years. The upper lobes are fibrotic and the lower lobes emphysematous. The pulmonary artery in each lung is shortened and its branches in the upper lobes are destroyed. In the lower lobes the vessels are narrowed due to emphysema.

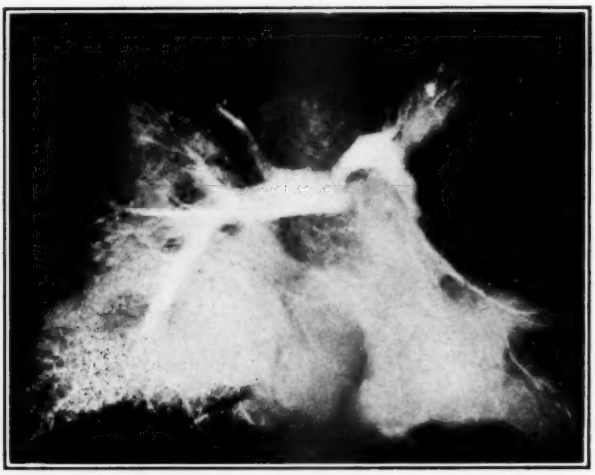

FIG. 4.—Case 9585, white male, aged 45, anthracite coal miner 26 years. The left lung has a large tuberculous cavity. The left lower lobe is fibrotic. Note the marked narrowing of the pulmonary artery near the cavity in the left lung.

of the pulmonary vessels due to sclerosis (Figs. 1 and 2). Somewhat similar sclerotic changes occur in the vessels of anthracosilicotic lungs due to the irritation of the coal and silica and due to intrapulmonary hypertension accompanying emphysema which almost always coexists with anthracosilicosis. We see in addition to sclerosis of the vessels diminution in number of the vessels in excavated areas (Figs. 3 and 4). In presence of such vascular changes the alterations, if any, that may occur in the pulmonary circulation present an interesting problem.

The present communication reports observations on the pulmonary circulation in 20 cases of unilateral pulmonary tuberculosis treated with artificial pneumothorax, 15 cases of pure anthracosilicosis and 10 cases of anthracosilicosis in association with pulmonary tuberculosis.

Method. The pulmonary circulation time devised by Winternitz, Deutsch and Brull,[3] using the bitter tasting property of sodium dehydrocholate, was employed with slight modification. Having rinsed the mouth the patient rested on the back for 5 minutes with the right arm raised to the level of his heart. Using a 19-gauge needle attached to a 5 cc. Luer syringe, 2 cc. of 20% sodium dehydrocholate was injected into the antecubital vein, taking not more than 2 seconds. The patient was instructed to signify the instant he noticed a bitter taste on his tongue. The interval between the injection and the bitter taste was taken as the pulmonary circulation time. Ten to 12 seconds as found in a group of normal adults was used as the normal standard time.

Results and Discussion. In the artificial pneumothorax group the pulmonary circulation time varied from 7 to 13 seconds, in the pure anthracosilicotic group 12 to 30 seconds and in the tuberculous anthracosilicotic group 11 to 60 seconds.

The Roentgen ray films of the lungs of these three groups of cases compared with the films of those which came to necropsy show no remarkable difference. From this we presume that the same vascular changes are present in the living as in the necropsied lungs. It is interesting, then, to note that the circulation time is practically normal in the artificial pneumothorax group. They presented no signs of respiratory or circulatory insufficiency. Dyspnea was felt by most of them only on exertion and none of them showed signs of cardiac decompensation.

In the pure anthracosilicotic group the circulation time was normal only in 2 cases. In the tuberculous anthracosilicotic group it was normal in 3 cases. In the rest of the cases in both groups the circulation time was distinctly increased and longer than that found in the artificial pneumothorax group. Dyspnea was not a prominent feature in those in whom the circulation time varied between 11 to 17 seconds. Dyspnea, however, was marked and constant when it was longer than 17 seconds. Cyanosis and edema of the ankles in addition to dyspnea became manifest when the circulation time

was found to be over 30 seconds. Slight dyspnea on exertion felt by those patients with a circulation time no longer than 17 seconds was due to emphysema coexisting with anthracosilicosis whereas marked dyspnea manifesting itself in those having longer circulation time was principally cardiac in origin. In this latter group cardiac enlargement as found by the physical examination, Roentgen ray and necropsy was a frequent finding.

The normal pulmonary circulation time as found in the artificial pneumothorax group and in a few cases of the anthracosilicotic group with or without pulmonary tuberculosis does not necessarily indicate that the pulmonary circulation in these cases is normal. The circulation time in these cases is no index of the volume of bloodflow through the collapsed, fibrotic or emphysematous lungs. We find that the velocity of fluid flowing through a shorter and narrower tube is faster than through a longer and wider tube. The quantity of fluid, however, passing through a larger and longer tube is greater. We know that in anthracosilicotic lungs with or without pulmonary tuberculosis and also in collapsed lungs, the vessels become narrowed and shortened due to sclerosis. In the absence of myocardial weakness, the velocity of bloodflow through such vessels may be practically normal but the volume flow will be less. In view of this, the absence of toxic symptoms in many cases of anthracosilicosis in association with pulmonary tuberculosis, as pointed out by Landis,[2] and amelioration of symptoms in satisfactory artificial pneumothorax cases may be in part due to decrease in the volume of bloodflow through the diseased lung.

Summary and Conclusion. 1. The pulmonary circulation is studied in pulmonary tuberculosis treated with artificial pneumothorax, pure anthracosilicosis and anthracosilicosis associated with tuberculosis.

2. Pulmonary circulation time is practically normal in artificial pneumothorax but usually prolonged in anthracosilicosis with or without pulmonary tuberculosis due largely to cardiac weakness.

3. It is suggested that regardless of normal circulation time in the artificial pneumothorax group and in a few cases of the anthracosilicotic group with or without pulmonary tuberculosis the volume of bloodflow through the diseased lungs may be decreased.

The writers desire to tender their thanks to Dr. Frank A. Craig and to Dr. Joseph Walsh for their valuable criticisms and permission to use the sanatorium material.

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ANGIOSPASTIC CLAUDICATION.*

WITH A REPORT OF SIX CASES.

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ONE of the most frequent complaints of patients who suffer from arterial disease is claudication. By claudication is meant any pain or cramp, often in the calves, sometimes in the toes or soles, less often in the thighs, initiated by exercise, and relieved promptly by rest. In addition, the patient may have other signs or symptoms of arterial insufficiency. Color changes of digits, trophic changes in the skin, nails and subcutaneous tissue, diminution of palpable arterial pulsations, decrease in temperature of the part, ischemia on elevation, rubor on dependency, and finally gangrene, all mark the extremity suffering from insufficient blood supply.

Differentiation Between Spasm and Occlusion as Factors in Peripheral Arterial Disease. Having determined that the peripheral arteries are at fault, the next problem is to decide whether the failing circulation is due to organic occlusion of vessels, to pure vasospasm, or to a combination of the two. This is determined by the accurate measurement of surface temperature by means of a thermocouple (Scott[6]), noting the temperature variations during vasomotor paralysis. It is now known that the sympathetic vasoconstrictor fibers do not pass to their areas of distribution with the blood-vessels. They accompany for the most part the peripheral sensory nerves, and supply areas very closely approximating the peripheral cutaneous sensory distribution.[9] Ablation of vasoconstrictor influence may be obtained by various methods. Among these may be mentioned 1, subarachnoid block; 2, conduction block of peripheral nerves;[7a,b] 3, sympathetic nerve block;[8] 4, general anesthesia;[7a] 5, use of high environmental temperature,[1] and 6, by soaking the upper extremities (for testing the feet) or the lower extremities (for testing the hands) in water at 43 to 45° C. This Clinic has had experience with only the first three methods, mostly, however, with conduction block of peripheral nerves, and thinks that peripheral nerve block is more logical from a theoretical standpoint, more desirable from the practical standpoint, and gives more consistently reliable information from the clinical standpoint, than other tests. Our experiences with this method and a fuller discussion of these points will be reported in an article to follow. When total vasoconstrictor paralysis has been induced in normal individuals the surface temperature of the affected regions rises to a certain level,

* Read in part, before the San Francisco County Medical Society, August 14, 1934.

irrespective of the original temperature. This is called the "normal vasodilatation level,"[7a] and is remarkably constant for the type of vasomotor study employed.

The response of the body to gradual arterial occlusion is the ablation of vasoconstrictor influence. This does not seem to occur in cases of arteriospasm. In individuals suffering from pure vasospasm, the surface temperature after novocaine block or general anesthesia rises to the normal vasodilatation level. In those suffering from pure occlusion there is little or no rise of surface temperature. In the combination of spasm and occlusion, there is a variable rise of temperature which is in direct proportion to the amount of spasm present.[4,7b] The difference between the maximum temperature obtained and the normal vasodilatation level is called the "occlusion index."[7a] The treatment varies in accordance with these findings.[4] In the author's experience, the response of skin temperatures, properly controlled and measured, is a most reliable index of the vasoconstrictor element. There may be diminution or absence of arterial pulsations in the foot and yet one may obtain a normal vasodilatation level. In such cases, if the pulsations become normal after vasoconstrictor paralysis, arteriospasm was undoubtedly the cause of the diminished pulsations. If the pulsations are unchanged in the presence of a normal vasodilatation level, it is probable that the collateral vessels are under vasomotor control to the point of permitting normal vasodilatation.

In differentiating the claudication due to arteriospasm from that due to arterial occlusion it is assumed that the presence of a normal vasodilatation level is sufficient evidence of the ability of the arterial tree to dilate to the same extent as occurs in vasoconstrictor paralysis in normal subjects. Although there is no doubt that the skin temperatures are directly proportional to the amount of blood flowing through the part, this gives no information as to the circulatory responses of the deeper tissues.

The pain of claudication is at times referred over sympathetic pathways.[2,5a,b] Blocking directly the sympathetic chain at the proper level gives information not only as to the presence or absence of occlusion, but also as to whether pain is referred over this system.[8]

In the past, the term claudication has been practically synonymous with occlusive disease. In examining a considerable number of cases complaining of claudication, I have found 6 which were on an arteriospastic basis. The clinical picture was similar in all.

Case Abstracts. Case 1.—C. S., a Russian housewife, aged 53, for the past year complained of claudication in both calves after walking exactly 1 block on the level, worse on the left side. She is a diabetic of 20 years' standing and also has high blood pressure.

Examination. All vessels of the lower extremities have normal pulsations except the right posterior tibial, which cannot be felt. There is a slight elevation ischemia on both sides, but no dependent rubor. Roentgen-rays show very slight calcification of the foot vessels on the right; moderate

on the left. However, in view of these excellent pulsations and the subsequent tests, the Roentgen ray findings are probably not significant. Claudication was induced on the left. During the pain, the toes were white and cadaveric, and the dorsalis pedis artery could not be palpated. After 1 minute rest, the pain disappeared and the normal color returned; soon afterward the dorsalis pedis pulsation could again be felt normally.

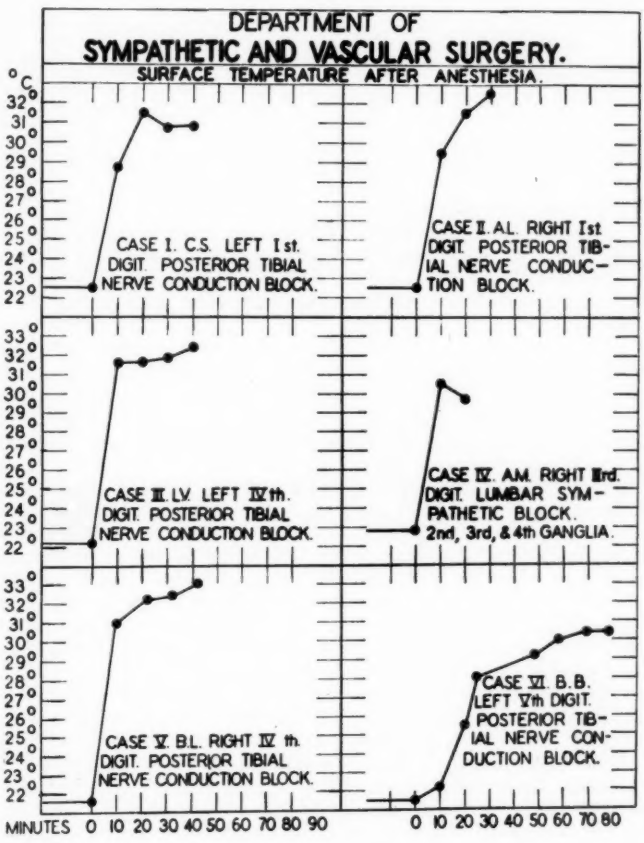
DEPARTMENT OF
SYMPATHETIC AND VASCULAR SURGERY.
SURFACE TEMPERATURE AFTER ANESTHESIA.
°C
CASE I. C.S. LEFT Ist. DIGIT. POSTERIOR TIBIAL NERVE CONDUCTION BLOCK.
CASE II. A.L. RIGHT Ist DIGIT. POSTERIOR TIBIAL NERVE CONDUCTION BLOCK.
CASE III. L.V. LEFT IVth. DIGIT. POSTERIOR TIBIAL NERVE CONDUCTION BLOCK.
CASE IV. A.M. RIGHT IIrd. DIGIT. LUMBAR SYMPATHETIC BLOCK. 2nd, 3rd, & 4th GANGLIA.
CASE V. B.L. RIGHT IV th. DIGIT. POSTERIOR TIBIAL NERVE CONDUCTION BLOCK.
CASE VI. B.B. LEFT Vth DIGIT. POSTERIOR TIBIAL NERVE CONDUCTION BLOCK.
MINUTES 0 10 20 30 40 50 60 70 80 90
0 10 20 30 40 50 60 70 80

CHART I.—Vasomotor studies on cases reported. The normal vasodilatation level for peripheral nerve conduction block is 30.5° C. That for sympathetic block is 31.5° C. The normal curve is a steep rise to the normal level. Slow rises are suggestive of arterial occlusion. The element of vasoconstrictor spasm is marked in each case.

There were normal vasodilatation responses to controlled posterior tibial nerve block in each foot (Chart I). This indicated that the symptoms were not due to arterial occlusion. One week later, during the vasodilatation following novocaine block of the left 2d, 3d and 4th lumbar sympathetic ganglia, she walked without pain, and it was impossible to produce ischemia of the foot or decrease of foot pulses by exercise. After 1½ hours, the vaso-

dilatation disappeared, and the condition present before injection returned. She failed to report for treatment.

CASE 2.—A. L., a Russian housewife, aged 67, complained of claudication in both calves after walking exactly $2\frac{1}{2}$ level blocks. For the past 20 years, she has had a marked swelling of both legs which is worse after walking and at night. She also suffers from hypertensive heart disease.

Examination. Revealed a brownish discoloration and swelling of the ankles and the lower half of both legs of the lymphatic type. No pulses were palpable in either foot. Both popliteal arteries had diminished pulsations. The femoral arteries pulsated normally. There was moderate elevation ischemia and mild dependent rubor in both feet. The right foot and lower leg were colder than the left, the change occurring abruptly 3 inches above the ankle.

Claudication was induced in both calves by exercise. Immediate inspection showed marked local ischemia of the lower two-thirds of both feet. As the pain disappeared the feet resumed the normal color. There was a normal vasodilatation response to bilateral posterior tibial nerve block (Chart I), showing that the symptoms were not due to occlusive arterial disease. During vasodilatation both dorsalis pedis and both posterior tibial arteries became palpable. Roentgen rays showed no calcification of leg or foot arteries.

The claudication was probably due to a pure arteriospasm. Diathermy to the lumbar sympathetics was advised, but she elected to go to a warmer climate for 2 weeks. She was considerably improved on her return and could walk 6 blocks without pain. Examination showed ischemia of the toes during the pain of claudication, as before. She took diathermy for 3 weeks and could then walk 9 blocks.

CASE 3.—B. B., male, aged 48, for the past 3 months has had attacks of dull cramp-like pain which began just below the knee posteriorly and extended to the front of the leg and finally the foot. The foot then became numb, helpless, and felt swollen. He was forced to rest. The symptoms were initiated only by exercise and relieved in about 30 seconds by rest; they occurred in either foot, but never both feet simultaneously. He can now walk only 1 level block rapidly. His work necessitates the carrying of heavy ice-cream freezers weighing as much as 75 pounds up many flights of steps daily. These attacks have caused him to discontinue employment.

Examination of the Extremities. The right popliteal pulse was diminished. All other pulsations were normal. The strength of the dorsalis pedis pulse was variable. There was no ischemia on elevation or rubor on dependency. Controlled thermocouple readings showed no abnormal temperature differences. Following posterior tibial nerve block, there were normal vasodilatation levels in both feet (Chart I), showing that symptoms were not due to vascular occlusion. During vasodilatation the dorsalis pedis pulsations increased, and he was able to climb rapidly four steep flights of steps without symptoms, whereas previously he could only climb one or two flights. Later, claudication was induced on the right. Prompt examination showed the right foot waxy, blanched, and cadaveric, and no pulsation of its dorsalis pedis; the left foot was slightly blanched and its dorsalis pedis diminished. One minute later the symptoms disappeared, the right foot resumed its normal color, and a few seconds later the dorsalis pedis could again normally be felt. Both feet were immersed in water at 16° C. for 10 minutes. Both remained pink. Claudication was again induced. The picture of ischemia again appeared on the right, whereas the left foot remained pink in marked contrast. The claudication in this patient is shown by the studies detailed above to be due to arteriospasm. Lumbar ganglionectomy was advised, but the patient refused. He has not returned since.

CASE 4.—A. M., male, aged 62, complained that for the past 3 months he has had claudication in both calves after walking 2 level blocks, worse on the right side. He has had flat feet, but was not relieved by arch supports fitted by an orthopedist. Several months ago, ulcers appeared on his legs and feet. These healed only a short time ago. He has had varicose veins of both legs for years.

Examination. On the *right side* the pulsation of the dorsalis pedis artery was slightly diminished, the posterior tibial absent, and the popliteal and femoral normal. There was slight elevation ischemia and mild dependent rubor of the anterior two-thirds of the foot. On the *left side* the pulsation of the dorsalis pedis, popliteal, and femoral arteries was normal; the posterior tibial was not felt. There was normal color on elevation; slight rubor on dependency, less than on the right. Neither leg had ulcers or gangrenous areas, but scars of the old ulcers were present on both legs and both feet. Both legs were the site of marked varicose veins, in some of which were areas of calcification.

Claudication was induced on the right by exercise. Coincident with its onset the right foot became blanched and the pulsation of its dorsalis pedis artery imperceptible. As the cramp subsided the color and the pulsation returned. There was no change in the color or the pulsations of the left foot; during exercise it retained the mild erythemia found on dependency.

A few days later, the second, third, and fourth right lumbar sympathetic ganglia were blocked with novocaine. During vasodilatation (Chart I), he jumped until exhausted, but neither claudication nor color changes appeared. After a slight rest he was also able to walk up three flights of building steps until exhausted, but had no cramps in his legs. These studies indicate that symptoms were probably due to arteriospasm. He refused diathermy and vasodilating drugs and has not been heard from since.

CASE 5.—B. L., a married woman, aged 70, for the past year complained of claudication in both legs, especially the left after walking one level block. Her feet have felt cold recently. There has been no ulceration or gangrene.

Examination. Showed the pulsation of both dorsalis pedis arteries present but slightly diminished, the left more so than the right. The posterior tibial arteries were not felt. The popliteal artery was not felt on the left; it was barely palpable on the right. Both femoral pulsations were normal. There was mild ischemia of the feet on elevation, but no rubor on dependency. During claudication, the feet were found to be cadaveric, the foot pulses absent. Normal color returned after 2 minutes' rest, but the pain was not relieved until about 3 minutes later when the foot pulses were again palpable.

There was a normal vasodilatation response (Chart I) on both sides to posterior tibial nerve block. Roentgengrams showed no calcification of foot vessels. A few days later, the second, third, and fourth lumbar sympathetic ganglia of both sides were blocked with novocaine. During the vasodilatation, she walked five blocks without pain. As soon as the vasodilatation disappeared she could walk only a half block without pain.

The above studies show that the claudication occurred in extremities capable of full vasodilatation and therefore it was primarily of a spastic nature. She obtained no relief from 3 weeks of diathermy to the lumbar sympathetics and did not report for 9 months when she complained of increased severity of claudication during the past 6 months. She could hardly walk at all. Both feet became numb and tingled, these symptoms progressively spreading up the calf. She had severe cramps at night. Examination showed no vessels palpable below the femorals in both lower extremities. The femoral pulses were slightly diminished. There was slight rubor of the right toes on dependency, otherwise no other abnormal vascular signs. The feet were warm. Vasomotor studies were repeated using pos-

terior tibial nerve block as before. Comparison with results of the 1934 test showed that the digits of the left foot reached a level only from 0.1 to 0.7° C. below that of 1934, whereas those of the right foot were from 2.9 to 3.6° C. below the 1934 level. Occlusive indices on the right ranged from 0.5 to 3.3. Roentgen rays of the feet, which were negative in 1934, showed barely perceptible calcification of the dorsalis pedis arteries. There was no question but that there was a change for the worse on the right side, and that the element of spasm was receding. On August 14, 1936, the right second, third, and fourth lumbar sympathetic ganglia were blocked with absolute alcohol. She was confined to bed since the injection because of severe pain due to the alcohol and entered the hospital September 1, 1936. The surface temperature rise following the injection was still present, and she had an anhidrosis of the entire right lower extremity and hyphidrosis of the left thigh. Since the alcohol injection she had been confined constantly to bed because of severe pain and is now (October 30, 1936) failing rapidly. It was therefore impossible to determine the effect of the alcoholic injection in this patient on her claudication.

Case 6.—A man, aged 80, complained that for the past 8 years he has had claudication in the left calf after walking 1 level block. For several months he has had attacks of numbness of the left leg. The femoral artery was faintly palpable on the left. All other arteries of this extremity were not felt to pulsate. On the right the femoral artery pulsation was normal, the popliteal was much diminished, and the foot artery pulsations were absent. There was no change on elevation, but on dependency rubor was slight to the ankle on the right, moderate to the ankle on the left. There were marked varicose veins on the right, slight on the left. On exposure of the feet to a constant room temperature of 70° for ½ hour there was a blotchy cyanosis of both feet from the ankle to the toes. The toes were markedly blanched. Posterior tibial nerve block on the left showed a normal vasodilatation level in the fifth toe, and very small occlusion indices on the other toes, ranging from 0.5 to 2.1 (Chart I). The arteries of the foot did not pulsate during the vasomotor block. Roentgen rays of both feet showed no arterial calcification. These studies indicated that arteriospasm was the factor of importance in the production of symptoms. Because of myocarditis and arterial hypertension, it was considered unwise to subject him to the exercise test. After 10 diathermy treatments to the lumbar spine the claudication disappeared. The patient died about 2 weeks later of pneumonia complicating a severe carbuncle of the neck.

This case is one in which a high vasodilatation level was present in all toes. Although Roentgen rays failed to show arterial calcification, there is a slight degree of arterial insufficiency as shown both in the absence of foot pulsations, and the response to nerve block. Arteriosclerotic degeneration may produce occlusion without calcification. In any event the ability of the arteries, either major or collateral, to dilate is amply shown by the response to vasomotor paralysis; the symptom of claudication must therefore be due primarily to arteriospasm.

Discussion. These cases had in common the symptom of claudication. The onset of claudication was associated with diminution of arterial pulsations and acute ischemia of the part. Relief was associated with return of the previous color and of palpability of pulses. All had normal or nearly normal vasodilatation levels. Roentgen rays usually showed no arterial calcification.

In 1932, Morton and Scott[4] reported 8 cases of claudication associated with normal or nearly normal vasodilatation levels;

5 were in cases of thrombo-angiitis obliterans; 1 had no evidence of organic arterial disease; 1 had definite evidence of arterial disease without evidence of calcification by Roentgen ray; and the last had definitely calcified foot and leg arteries with undoubted signs of occlusive arterial disease. No mention was made of the behavior of the foot pulses or the occurrence of color changes of the feet coincident with claudication or immediately after the cessation of claudication.

In none of the cases reported herein, was there evidence of thrombo-angiitis obliterans. Some cases showed evidence of organic arterial disease. Angiospastic claudication may occur in patients who have no organic arterial disease, and it may also occur as a symptom of early organic arterial disease. My Case 5 is a case in point.

The following data were obtained from the analysis of the 6 cases reported herein (Table 1). Their average age was 63.3 years. There were 3 males, 3 females. Tobacco was not used by 4 patients, moderately used by 2. The average duration of symptoms was 27 months; only 2 had symptoms for over a year. Moderate elevation ischemia was noted in both extremities in 3 cases, in one extremity in 2 cases; it was absent in only 1 case. Mild rubor was present in 4 cases; in all but 1 it was bilateral. There was a history of ulceration in 1 (A. L.); in this case, varicose veins may have been the prime factor. No case had gangrene, past or present. The dorsalis pedis arteries were palpable in 5 cases, in 1 (A. L.) only after nerve block. The posterior tibial arteries were palpable in 3 cases; 1 unilaterally, 1 bilaterally, and 1 (A. L.) only during vasoconstrictor paralysis. There was no constant relationship between the side of more pronounced symptoms and the palpability of vessels. Varicose veins were present in 3 cases. Roentgen rays of the feet were taken in 4 cases; in 3 there was no visible calcification; in 1 (C. S.) there was mild calcification probably of little significance. Lumbar sympathetic novocaine block was done on 3 cases; in each of these the symptoms were relieved during the block. One case (B. B.) was relieved during posterior tibial nerve block.

In analyzing the significance of arterial pulsations, one should remember that there is a variation which is within normal limits. In my experience the presence and strength of the pulsation of the dorsalis pedis artery is the most reliable. The posterior tibial artery is the most variable, and its diminution or absence is not so significant as that of the dorsalis pedis artery. The popliteal artery is often difficult to feel, but its presence is more constant in normal extremities than the posterior tibial.

Treatment. Treatment should at first be conservative. Two of my cases obtained relief from diathermy to the lumbar region. Vasodilating drugs should be tried. Tobacco should be eliminated.

Table 1.—Case Data.*

Case.	Age.	Sex.	Tobacco.	Duration of claudication.	Walking distance—claudication.	Side.	Intensity of symptoms.	Elevation ischemia.	Dependent rubor.	Sudden temp. change.	Trophic dist.	Color changes.	Ulceration.	Gangrene.	Arterial pulsations.				Occlusive index.	Varicose veins.	Edema.	Calcification of arteries in Roentgen ray.	Effect of claudication on		Effect of vasomotor paralysis on symptoms.
															Dorsalis pedis.	Post. tibial.	Popliteal.	Femoral.					Appearance of foot.	Dorsalis pedis pulse became	
1 C. S.	53	F	○	1 yr.	One level block	R	++	+	○	○	Nails	○	○	○	+++	○	+++	+++	○	○	○	+	Not tested		
						L	+++	+	○	○	Nails	○	○	○	+++	+++	+++	+++	○	○	○	++	Cadaveric ischemia of toes coincident with claudication. Return of normal color with relief	○	Impossible to produce claudication, pulse changes, or ischemia during lumbar sympathetic novocaine block.
2 A. L.	67	F	○	2½ mo.	2½ level blocks	R	+++	++	+	Cold below 3 inch above ankle	○	Brown discoloration of ankles	○	○	○	○	++	+++	○	++	Lym. +++ type	○	Ischemia both feet. Return normal color with relief of claudication	○	Dorsalis pedis and post tibial pulses became palpable +++ during vasomotor paralysis.
						L	+++	++	+	○	○		○	○	○	○	++	+++	○	++	Lym. +++ type	○		○	
3 B. B.	48	M	½ sac daily	10 mo.	1–2 flights steps with load	R	+++	+	+	○	○	○	○	○	++	+++	+	+++	○	○	○		Cadav. isch. of foot coin. with claud. Return normal color with relief.	○	Dorsalis pedis pulse +++ during vasomotor paralysis. Unable to produce claudication, pulse changes or ischemia during vasomotor paralysis.
						L	+++	○	○	○	○	○	○	○	+++	+++	+++	+++	○	○	○		Blanching after exercise.		
4 A. M.	62	M	40 cigarettes daily	3 mo.	2 level blocks	R	+++	+	+	○	○	○	○	○	++	○	+++	+++	○	+++	○		Cadaveric ischemia of foot coincident with claudication. Return of normal color with relief	○	Unable to produce claudication, pulse changes, or ischemia during lumbar sympath. novo. block.
						L	++	○	+	○	○	○	○	○	+++	○	+++	++	○	+++	○		Claudication not induced		
5 B. L.	70	F	○	1 yr.	One level block	R	++	+	○	○	○	○	○	○	++	○	+	+++	○	○	○	○	Cadaveric ischemia both feet coincident with claudication Return of normal color with relief	○	Unable to produce claudication, pulse changes, or ischemia during lumbar sympathetic novocaine block.
						L	+++	+	○	○	○	○	○	○	+	○	○	+++	○	○	○	○		○	
6 J. C.	80	M		8 yrs.	One level block	R	○	○	+	○	○	○	○	○	○	○	+	+++	Not determined	+++	○	○	Test not done because of bad heart		Test not done.
						L	+++	○	++	○	○	○	○	○	○	○	○	+	0 to 2.1	+	○	○			Test not done.

* ○ = symptom absent, sign absent, pulsation absent.
+ = symptom slight, sign mild, pulsation barely felt.
++ = symptom moderate, sign moderate, pulsation easily felt, but below normal force.
+++ = symptom severe, sign marked, pulsation normal.

The extremities should be kept warm constantly. If conservative measures fail and the symptoms are incapacitating, the lumbar sympathetic ganglia should be blocked with novocaine for diagnostic purposes. If this brings relief, lumbar ganglionectomy is advised. Vasomotor studies should be done every 3 months. Roentgen rays of foot vessels should be taken every 6 months. If the vasodilatation level recedes, lumbar ganglionectomy should be done to promote collateral circulation and to prevent as far as possible the occurrence of organic arterial insufficiency. Alcoholic injection of the lumbar sympathetics may be used in place of ganglionectomy in patients who are poor risks for surgery, but often the disability resulting from alcohol injection is much greater than that resulting from surgery.

Summary. 1. Six cases are reported in which the symptom of claudication was shown to be due to arteriospasm.

2. The onset of claudication is associated with acute ischemia of the foot and diminution or absence of foot pulsations; relief is associated with return of normal color and palpability of foot arteries.

3. All cases have normal or nearly normal vasodilatation responses to properly controlled vasomotor paralysis. In 1 case previously imperceptible foot pulses became palpable during vasomotor paralysis. Evidence indicates that the collateral circulation may be under vasomotor influence to the point of allowing normal vasodilatation.

4. Roentgen rays of the feet were taken in 4 cases. In 3 they showed no calcification of vessels; in 1 there was slight calcification of little significance.

5. Treatment should be conservative. If this fails, the response to diagnostic novocaine block will determine the advisability of lumbar ganglionectomy. The latter procedure should be advised in good risks which are incapacitated by the symptoms and which are relieved by diagnostic block. If vasomotor studies show receding of the vasodilatation level, lumbar ganglionectomy should be done. Poor surgical risks may be treated by alcohol injection of the lumbar sympathetic chain.

6. The term "Angiospastic Claudication" is descriptive of the syndrome and distinguishes it from the claudication of occlusive arterial disease.

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CHANGES IN THE ELECTROCARDIOGRAM AS CRITERIA OF INDIVIDUAL CONSTITUTION DERIVED FROM ITS PHYSIOLOGICAL PANEL.

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Our earlier published studies of the human organism as a whole dealt chiefly with morphology; and it has been our experience that within limits persons afflicted with the same illness exhibit in common a characteristic morphology. In other words, the nature of the anatomic panel may often indicate a relationship between total personality and disease. We have long considered whether correlations may likewise exist between disease proclivity and characters within the physiologic panel. It seemed possible that certain physiologic techniques which have rendered dependable evidence of pathologic function might also illuminate normal individual differences in the special qualities of separate organs. For surely we must assume that it is the mutual coöperation of these organs which proclaim at once the unity and personal identity of each individual.

Observations bearing on this concept are not new in medicine. Thus, for example, Laignel-Levastine and Maingot[5] described various forms of diaphragmatic motion, as seen by fluoroscope, which showed high correlation with the nature of the whole man and his special disease potential. Speaking of diaphragmatic movements they state: "There exists an internal physiognomy which from the standpoint of individuality surpasses the external. External gestures are consciously appreciated and controlled; the spontaneous movement of the diaphragm is subconscious." According to Nielsen and Roth,[6] spirograms can be used to identify at least nine different types of persons. Many of these spirogram patterns are hereditary and indicate certain predispositions in the person.

Cardiologists have known that the form of the electrocardiographic curve, and the time relationship of its component parts, correlates with age. Furthermore, Cohn and Swift[2] state that the general form of the electrocardiogram is relatively constant in normal persons over long periods of time. In his Nobel prize oration, also, Einthoven,[4] showed that if there had been no change in the heart's condition during long periods of months, or even years, the electrocardiographic records were practically identical. He illustrated this by two records taken 31 years apart from a patient who had an unchanging lesion for that whole period of time (Fig. 1). Cohn[2] has kindly supplied us with the records shown in Figures 2 and 3.

In the records of 1933, 1936 and 1937 the 3 leads were synchronously recorded by the use of 3 galvanometers. Apparently the recorded voltage is in every case slightly lower by this technique than when each lead is taken separately as in the earlier electrocardiograms. In each case the adherence in the later record to the individual's initial pattern is clear. Only in the *T* wave, which is perhaps the most labile component in the whole complex do striking variations appear. In Figure 2 (Case 3) a difference in the relative positions of the *Q* and *S* waves also appears. Whether it can be said that an electrocardiogram is unique for each person, or perhaps for a type of human being, is a question. At least there is at present little information available on the point.

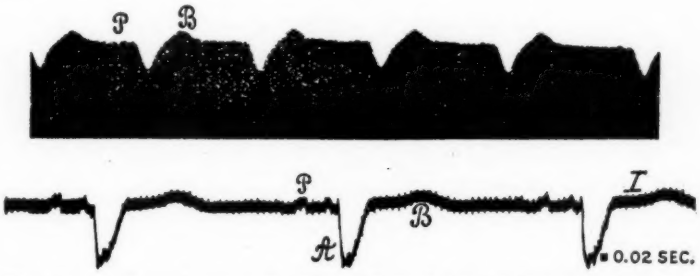

FIG. 1.—Einthoven's comparison of capillary electrometric curve taken 1894 (Lead I), and Ekg (Lead I) of same case taken 31 years later, in 1925.

Method. In order to test the possibility that the electrocardiographic record might provide a criterion of constitution from the physiologic panel, two groups of invalids, peptic ulcer and gall bladder, all having normal electrocardiograms were studied.

For control observations on age variation of the *P–R* and *Q–T* intervals, as well as pulse rate, the electrocardiograms of 578 individuals with normal records, selected from the general hospital population both male and female, were used. These were divided into 6 age decades, from 10 to 69 (Table 1). All calculations in the tables are for convenience expressed in terms of the actual value times 100. For the comparative study of ulcer and gall-bladder patients only males are being reported upon at present.

In the ulcer series there are 107 persons divided into 4 age decades, from 20 to 59 years. The decade groups though small are nevertheless sufficiently large for statistical validity. In the gall-bladder series there are only 35 males in all.

The P–R Interval. It is apparent from Figure 4 that among hospital males with normal electrocardiograms there is a gradual lengthening of the *P–R* interval up to and including the sixth decade. In the seventh decade there is a shortening again, but barely of statistical significance. The female curve follows almost the same line until the sixth decade. At this time, unlike the males, the *P–R* interval becomes shorter so that as between males and females in the sixth decade there is a significant difference*

* A difference between two compared means is significant when that difference is three or more times its probable error.

in the mean length of the *P–R* interval (Table 2). In the seventh decade the female curve rises again well above that of the males though not significantly.

The behavior of the *P–R* interval in the ulcer people is striking. Thus in the third decade the difference between the ulcer group

TABLE 1.—COMPARISON OF *P–R* INTERVALS OF HOSPITAL MALE AND FEMALE AGE GROUPS AND ULCER AND GALL-BLADDER AGE GROUPS.

Group.	Age in years.	No. of cases.	Range.	Mean and P E.* (hundredths of seconds)	S D* and P E.	V* and P E.
Male.						
Hosp.	10–19	40	12–19	14.78 ± 0.17	1.56 ± 0.12	10.55 ± 0.80
Hosp.	20–29	35	12–19	15.29 ± 0.22	1.89 ± 0.15	12.36 ± 1.00
Hosp.	30–39	43	13–20	15.58 ± 0.14	1.40 ± 0.10	8.98 ± 0.65
Hosp.	40–49	40	12–20	15.95 ± 0.18	1.67 ± 0.13	10.47 ± 0.79
Hosp.	50–59	51	12–19	16.33 ± 0.14	1.48 ± 0.10	9.06 ± 0.60
Hosp.	60–69	54	12–19	15.70 ± 0.16	1.69 ± 0.11	10.76 ± 0.70
Total male	..	263	12–20	15.65 ± 0.07	1.69 ± 0.05	10.80 ± 0.32
Ulcer	20–29	20	13–20	17.00 ± 0.30	2.02 ± 0.22	11.88 ± 1.27
Ulcer	30–39	44	13–22	17.14 ± 0.21	2.10 ± 0.15	12.25 ± 0.88
Ulcer	40–49	23	13–18	16.04 ± 0.17	1.20 ± 0.12	7.48 ± 0.74
Ulcer	50–59	20	13–19	16.45 ± 0.25	1.66 ± 0.18	10.09 ± 1.08
Total ulcer	..	107	13–22	16.75 ± 0.12	1.90 ± 0.09	11.34 ± 0.52
Total gall bladder	30–59	35	13–20	15.66 ± 0.19	1.70 ± 0.14	10.86 ± 0.88
Female.						
Hosp.	10–19	59	12–19	14.70 ± 0.13	1.49 ± 0.09	10.14 ± 0.63
Hosp.	20–29	60	12–19	15.02 ± 0.14	1.64 ± 0.10	10.92 ± 0.67
Hosp.	30–39	54	12–20	15.94 ± 0.18	1.93 ± 0.12	12.11 ± 0.79
Hosp.	40–49	56	12–19	15.68 ± 0.17	1.85 ± 0.12	11.80 ± 0.75
Hosp.	50–59	49	12–20	15.57 ± 0.18	1.87 ± 0.13	12.01 ± 0.82
Hosp.	60–69	37	12–19	16.24 ± 0.19	1.73 ± 0.14	10.65 ± 0.84
Total female	..	315	12–20	15.46 ± 0.07	1.83 ± 0.05	11.84 ± 0.32

* P E = Probable error; S D = Standard deviation; V = Variation.

TABLE 2.—DIFFERENCES OF MEANS OF MALE AND FEMALE SUBGROUPS WITH VALUE IN TERMS OF THE PROBABLE ERROR.

Subgroup.	Female* / Male Difference.	X P E.	
P–R Interval.			
Age 10–19	−0.08	−0.38	
Age 20–29	−0.27	−1.04	
Age 30–39	+0.36	+1.56	
Age 40–49	−0.27	−1.07	
Age 50–59	−0.76	−3.30	(Significant)
Age 60–69	+0.54	+2.16	
Total	−0.19	−1.90	
Q–T Interval.			
Age 10–19	−0.33	−1.06	
Age 20–29	−0.36	−0.90	
Age 30–39	−0.49	−1.40	
Age 40–49	−0.26	−0.72	
Age 50–59	−0.92	−2.70	
Age 60–69	−0.58	−1.45	
Total	−0.66	−4.12	(Significant)
Pulse Rate.			
Age 10–19	+5.90	+4.01	(Significant)
Age 20–29	+5.95	+3.63	(Significant)
Age 30–39	+4.80	+2.80	
Age 40–49	+3.10	+2.15	
Age 50–59	+5.90	+3.62	(Significant)
Age 60–69	+0.60	+0.34	
Total	+4.45	+6.64	(Significant)

* In this and other similarly expressed fractions the group above the line is compared with that below.

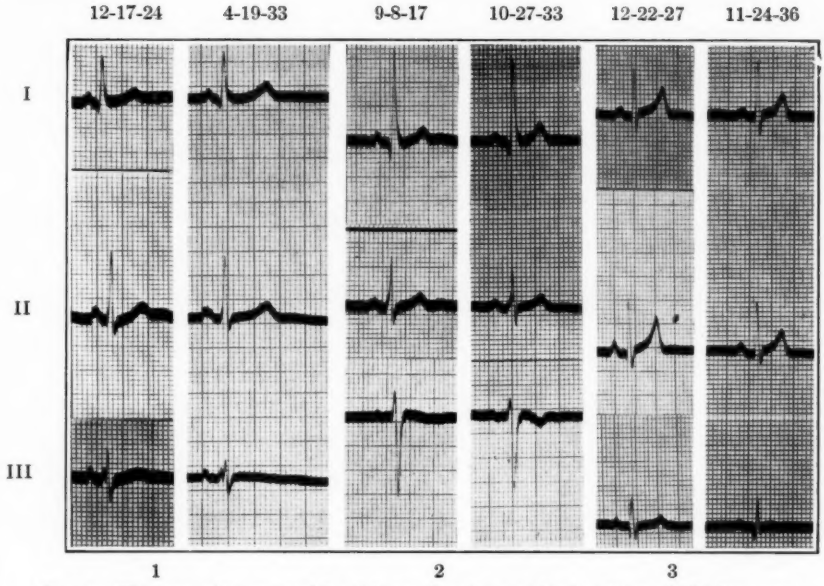

FIG. 2.—Electrocardiograms of 3 subjects, showing constant pattern similarity over 9 to 16 years.

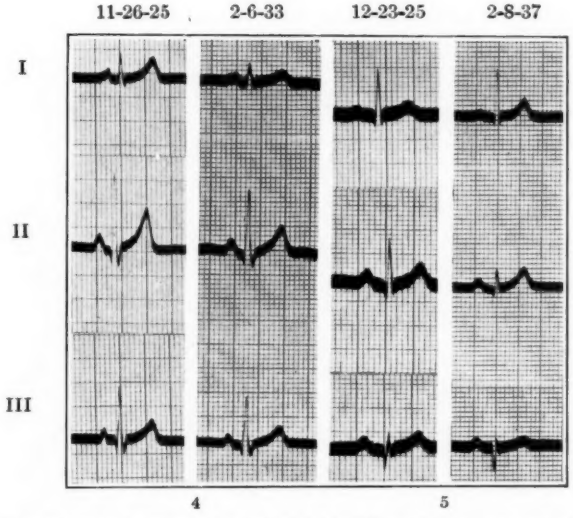

FIG. 3.—Electrocardiograms of 2 patients showing constant pattern similarity over 8 and 12 years.

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mean and control group mean is significant to the extent of being 4.62 times its probable error. In the fourth decade this figure rises to 6.24 times the probable error (Fig. 4 and Table 3). But here a

TABLE 3.—DIFFERENCES OF MEANS OF HOSPITAL AND ULCER MALES IN THE VARIOUS AGE GROUPS WITH VALUE IN TERMS OF THE PROBABLE ERROR.

Age group.	Ulcer / Hospital Difference.	X P E.	
P–R Interval.			
Age 20–29	+1.71	+4.62	(Significant)
Age 30–39	+1.56	+6.24	(Significant)
Age 40–49	+0.09	+0.36	
Age 50–59	+0.12	+0.41	
Total	+0.91	+6.50	(Significant)
Q–T Interval.			
Age 20–29	+2.36	+4.14	(Significant)
Age 30–39	+0.81	+2.31	
Age 40–49	+0.46	+1.04	
Age 50–59	+1.69	+3.60	(Significant)
Total	+1.03	+4.48	(Significant)
Pulse Rate.			
Age 20–29	−8.30	−4.05	(Significant)
Age 30–39	−6.15	−3.53	(Significant)
Age 40–49	+0.50	+0.25	
Age 50–59	−11.80	−6.56	(Significant)
Total	−5.85	−5.98	(Significant)

sharp change occurs, and in the fifth and sixth decades we find that the *P–R* interval of the ulcer people returns to the average determined in hospital series.

Because the number of males with gall-bladder disease is too small to divide into decade groups, they have been massed. The mean *P–R* interval for this series which comprises three decades is 15.66. This figure agrees statistically with that for the hospital controls. It appears therefore that ulcer people, especially during the two decades when the onset of the disease is most frequent tend to have significantly long *P–R* intervals, whereas the gall-bladder people do not.

So far as rate is concerned the well-established fact that females in general have faster pulse rates than males is clearly shown in the curves for the hospital controls (Fig. 4). It is interesting that both ulcer and gall-bladder people have pulse rates slower than those of the hospital series. Almost the slowest rates in both groups are found in the youngest age decades. In this connection it is worthy of note that sinus arrhythmia is definitely more common in the third and fourth decade ulcer people than in the same age groups of the hospital control series. One other point of interest concerning pulse rate is the extremely low count in the 50–59 year old ulcer males (Fig. 4 and Table 4).

The Q–T Interval. The *Q–T* interval (Fig. 4 and Table 5) shows a more or less regular lengthening of the period in both sexes through the six decades from 10 to 69 years. Among the controls the difference between the *Q–T* mean value in the second decade and the

TABLE 4.—COMPARISON OF PULSE RATE OF HOSPITAL MALE AND FEMALE AGE GROUPS, ALSO OF ULCER AND GALL-BLADDER AGE GROUPS.

Groups.	Age in years.	No. of cases.	Range.	Mean and P E.	S D and P E.	V and P E.
Male.						
Hosp.	10–19	40	50–100	80.10 ± 1.02	9.60 ± 0.72	11.98 ± 0.90
Hosp.	20–29	35	55– 95	75.30 ± 1.28	11.20 ± 0.90	14.87 ± 1.20
Hosp.	30–39	43	50–100	78.05 ± 1.37	13.30 ± 0.97	17.04 ± 1.24
Hosp.	40–49	40	55–100	75.40 ± 1.07	10.00 ± 0.75	13.26 ± 1.00
Hosp.	50–59	51	50–100	77.30 ± 1.27	13.45 ± 0.90	17.40 ± 1.16
Hosp.	60–69	54	50–105	78.00 ± 1.30	14.20 ± 0.92	18.20 ± 1.18
Total male	..	263	50–105	77.45 ± 0.52	12.40 ± 0.36	16.01 ± 0.47
Ulcer	20–29	20	45– 86	67.00 ± 1.60	10.60 ± 1.13	15.82 ± 1.69
Ulcer	30–39	44	55–100	71.90 ± 1.07	10.50 ± 0.75	14.60 ± 1.05
Ulcer	40–49	23	59–100	75.90 ± 1.68	11.95 ± 1.18	15.74 ± 1.56
Ulcer	50–59	20	42– 84	65.50 ± 1.28	8.50 ± 0.91	12.98 ± 1.38
Total ulcer	..	107	42–100	70.75 ± 0.72	11.10 ± 0.51	15.69 ± 0.72
Total gall bladder	..	35	50– 90	71.55 ± 1.25	11.00 ± 0.89	15.37 ± 1.24
Female.						
Hosp.	10–19	59	50–110	86.00 ± 1.06	12.05 ± 0.75	14.01 ± 0.87
Hosp.	20–29	60	54–100	81.25 ± 1.02	11.75 ± 0.72	14.46 ± 0.89
Hosp.	30–39	54	55–100	82.85 ± 1.02	11.15 ± 0.72	13.46 ± 0.87
Hosp.	40–49	56	50–100	78.50 ± 0.96	10.70 ± 0.68	13.63 ± 0.87
Hosp.	50–59	49	60–100	83.20 ± 1.03	10.70 ± 0.73	12.86 ± 0.88
Hosp.	60–69	37	55–105	78.60 ± 1.16	10.50 ± 0.82	13.36 ± 1.05
Total female	..	315	50–110	81.90 ± 0.44	11.55 ± 0.31	14.12 ± 0.38

TABLE 5.—COMPARISON OF MEANS OF *Q–T* INTERVAL OF HOSPITAL MALE AND FEMALE AGE GROUPS, ALSO OF ULCER AND GALL-BLADDER AGE GROUPS.

Group.	Age in years.	No. of cases.	Range.	Mean and P E.	S D and P E.	V and P E.
Male.						
Hosp.	10–19	40	28–39	33.75 ± 0.22	2.06 ± 0.16	6.10 ± 0.46
Hosp.	20–29	35	30–40	34.54 ± 0.31	2.69 ± 0.22	7.79 ± 0.63
Hosp.	30–39	43	30–42	34.21 ± 0.25	2.41 ± 0.18	7.04 ± 0.51
Hosp.	40–49	40	30–45	35.15 ± 0.28	2.63 ± 0.20	7.48 ± 0.56
Hosp.	50–59	51	29–42	35.41 ± 0.27	2.86 ± 0.19	8.08 ± 0.54
Hosp.	60–69	54	31–47	36.15 ± 0.30	3.30 ± 0.21	9.13 ± 0.59
Total male	..	263	28–47	34.96 ± 0.12	2.85 ± 0.08	8.15 ± 0.24
Ulcer	20–29	20	32–44	36.90 ± 0.48	3.19 ± 0.34	8.64 ± 0.92
Ulcer	30–39	44	29–40	35.02 ± 0.23	2.24 ± 0.16	6.40 ± 0.46
Ulcer	40–49	23	31–40	35.61 ± 0.34	2.46 ± 0.24	6.91 ± 0.69
Ulcer	50–59	20	32–41	37.10 ± 0.38	2.49 ± 0.26	6.71 ± 0.72
Total ulcer	..	107	29–44	35.89 ± 0.18	2.69 ± 0.12	7.50 ± 0.34
Total gall bladder	..	35	32–44	38.17 ± 0.32	2.79 ± 0.22	7.31 ± 0.59
Female.						
Hosp.	10–19	59	28–44	33.42 ± 0.22	2.50 ± 0.16	7.48 ± 0.46
Hosp.	20–29	60	29–41	34.18 ± 0.25	2.88 ± 0.18	8.42 ± 0.52
Hosp.	30–39	54	29–40	33.72 ± 0.24	2.67 ± 0.17	7.92 ± 0.51
Hosp.	40–49	56	28–42	34.89 ± 0.22	2.40 ± 0.15	6.88 ± 0.44
Hosp.	50–59	49	31–39	34.49 ± 0.21	2.14 ± 0.14	6.20 ± 0.42
Hosp.	60–69	37	28–39	35.57 ± 0.26	2.39 ± 0.19	6.72 ± 0.53
Total female	..	315	28–44	34.30 ± 0.10	2.62 ± 0.07	7.64 ± 0.20

average for the whole age span is significant. This is also true of the seventh decade (Table 6). Among the ulcer people those in the third decade show a significant lengthening of the *Q–T* interval. But this is not so in the 30–39 age group. In this connection it will be observed that at this age period there is no parallel change in the *P–R* value which remains high (Fig. 4 and Table 3).

Among gall-bladder people, however, an extremely long *Q–T*

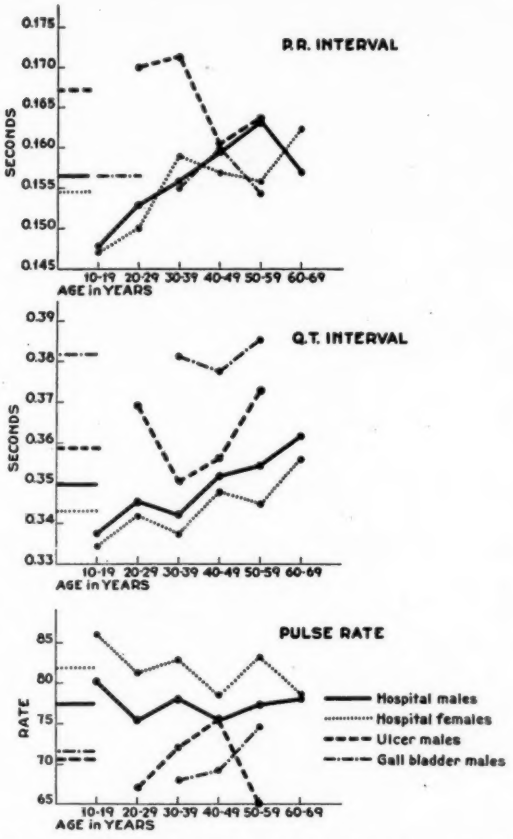

FIG. 4.—The *P–R* and *Q–T* interval and the pulse rate means of normal (male and female) and of ulcer and gall-bladder males electrocardiograms showing changes through six decades. Note: The short horizontal sample key lines at the left of the graphs indicate the means of each total series.

TABLE 6.—DIFFERENCES OF *Q–T* INTERVALS OF HOSPITAL CONTROL SUBGROUPS WITH VALUE IN TERMS OF THE PROBABLE ERROR.

Subgroup.	Subgroup / Total Series. Difference.	X P E.	
Male.			
Age 10–19	−1.21	−4.03	(Significant)
Age 20–29	−0.42	−1.31	
Age 30–39	−0.75	−2.59	
Age 40–49	+0.19	+0.63	
Age 50–59	+0.45	+1.67	
Age 60–69	+1.19	+4.58	(Significant)
Female.			
Age 10–19	−0.88	−3.82	(Significant)
Age 20–29	−0.12	−0.52	
Age 30–39	−0.58	−2.42	
Age 40–49	+0.59	+2.46	
Age 50–59	+0.19	+0.76	
Age 60–69	+1.27	+4.38	(Significant)

interval is the striking characteristic. The mean of this measurement for the whole group of 35 individuals spanning third, fourth and fifth decades is 0.382 sec. The difference between this figure and the mean for the same age groups of the hospital control series is 9 times its probable error (Fig. 4, Table 7). This is a high degree of significance and can in no way be attributed to chance.

TABLE 7.—DIFFERENCES OF MEANS OF GALL-BLADDER MALES AND HOSPITAL MALES WITH VALUE IN TERMS OF THE PROBABLE ERROR.

	Gall-bladder Males, Age 30–59 / Hospital Males, Age 30–59		
	Difference.	X P E.	
P–R interval	−0.32	−1.52	
Q–T interval	+3.22	+9.20	(Significant)
Pulse rate	−5.39	−3.74	(Significant)

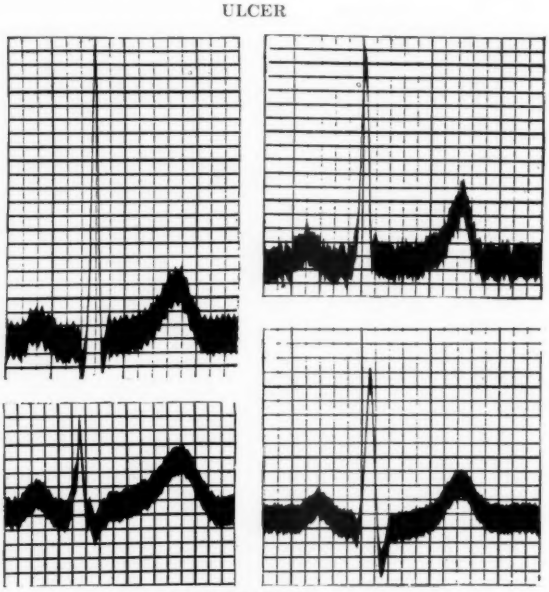

FIG. 5.—Comparison of complex forms (Lead II) from ulcer and gall-bladder people.

Aside from the measurable parts of the electrocardiograms, it is possible we believe to recognize differences of contour between those from ulcer and those from gall-bladder subjects. In general, the form of the curve from ulcer people is steeper, more abrupt; whereas the waves in those from gall-bladder people give the impression of being smoother and more rolling in character (Fig. 5). The descending limb of the *T* waves perhaps best emphasizes this point. In the ulcer group the descent is very steep; in the gall-bladder subjects

its downward slant is more gradual. In this respect the *T*-wave form of the latter group suggests that seen in records from persons afflicted with hyperthyroidism.*

TABLE 8.—DIFFERENCES OF *P–R* INTERVALS OF HOSPITAL CONTROL SUBGROUPS AND TOTAL SERIES WITH VALUE IN TERMS OF THE PROBABLE ERROR.

Subgroup / Total Series	Difference.	X P E.	
Male.			
Age 10–19	−0.87	−4.83	(Significant)
Age 20–29	−0.36	−1.89	
Age 30–39	−0.07	−0.41	
Age 40–49	+0.30	+1.67	
Age 50–59	+0.68	+4.25	(Significant)
Age 60–69	+0.05	+0.31	
Female.			
Age 10–19	−0.76	−4.75	(Significant)
Age 20–29	−0.44	−2.59	
Age 30–39	+0.48	+2.82	
Age 40–49	+0.22	+1.38	
Age 50–59	+0.11	+0.65	
Age 60–69	+0.78	+3.90	(Significant)

TABLE 9.—DIFFERENCES OF PULSE RATES OF HOSPITAL CONTROL SUBGROUPS AND TOTAL SERIES WITH VALUE IN TERMS OF THE PROBABLE ERROR.

Subgroup / Total Series	Difference.	X P E.	
Male.			
Age 10–19	+2.65	+2.01	
Age 20–29	−2.15	−1.52	
Age 30–39	+0.60	+0.47	
Age 40–49	−2.05	−1.55	
Age 50–59	−0.15	−0.13	
Age 60–69	+0.55	+0.48	
Female.			
Age 10–19	+4.10	+4.06	(Significant)
Age 20–29	−0.65	−0.65	
Age 30–39	+0.95	+0.90	
Age 40–49	−3.40	−3.27	(Significant)
Age 50–59	+1.30	+1.18	
Age 60–69	−3.30	−2.58	

TABLE 10.—MEANS OF HOSPITAL MALES OF GROUPED AGES, 20–59 AND 30–59, USED FOR COMPARISON WITH ULCER AND GALL-BLADDER MALES OF SIMILAR GROUPED AGES.

Group.	Age in years.	No. of cases.	Range.	Mean and P E.	S D and P E.	V and P E.
P–R Interval.						
Hosp.	20–59	169	12– 20	15.84 ± 0.08	1.65 ± 0.06	10.42 ± 0.38
Hosp.	30–59	134	12– 20	15.98 ± 0.09	1.55 ± 0.06	9.70 ± 0.40
Q–T Interval.						
Hosp.	20–59	169	29– 45	34.86 ± 0.14	2.70 ± 0.10	7.74 ± 0.28
Hosp.	30–59	134	29– 45	34.95 ± 0.15	2.66 ± 0.11	7.61 ± 0.31
Pulse Rate.						
Hosp.	20–59	169	50–100	76.60 ± 0.64	12.30 ± 0.45	16.06 ± 0.59
Hosp.	30–59	134	50–100	76.94 ± 0.73	12.60 ± 0.52	16.38 ± 0.67

Comment. The significance of these findings is not clear, especially with regard to the prolonged *Q–T* interval found among gall-bladder folk. We shall investigate this point further. So far as the marked prolongation of the *P–R* interval in the ulcer group is

* Though not specifically referred to in the text, Tables 8, 9 and 10 are published in order to present the complete statistical analysis.

concerned, we have supposed that like the sinus arrhythmia and slow pulse rate it expresses a strong vagus influence. Supporting this notion is the recent work of Bruenn,[1] showing that the prolonged conduction time in acute rheumatic fever is almost wholly due to vagus effect. This prolongation, he found, could be abolished either by atropine or under the stress of emotional excitement.

In this connection attention should be called to the highly nervous state in which ulcer patients who are bleeding or in great pain enter the hospital, and indeed, to the swift energetic responses they make to life in general. Pulse rates observed on admission are invariably high. Only after the initial storm is over, and when the patient is free from pain and his blood and confidence restored, does the pulse rate fall to its own constitutional level. This process requires about 3 weeks.

We desire however to make quite clear that we do not conceive of these electrocardiographic findings as expressing a secondary effect of the ulcer. Rather do we regard the slow pulse, sinus arrhythmia and prolonged $P–R$ interval as correlates of the ulcer and, like it, possibly indicating the peculiar vagotonicity of the ulcer subject. And here there seems perhaps to be a paradox. For it is well known that ulcer people often show wide palpebral fissures, easily sweating palms, rapid heart rate and general nervousness. We are inclined to believe however that the whole autonomic nervous system in people of ulcer constitution is high tension and labile, but that there is a special emphasis upon the parasympathetic division. Thus when fear, or the need of security suddenly impinges upon the consciousness of such a person the whole autonomic mechanism goes violently into action. Immediate effects of sympathetic stimulation appear—such as widened palpebral fissure, sweating, rapid pulse. But then there supervenes an equally strong and more prolonged vagus activity. This not only outlasts the sympathetic effects but may indeed specifically express the peculiar constitution of ulcer people.

There has been increasing support for the notion that the vagus nerve has much to do with ulcer production. The literature on the subject, which is very extensive, has been recently thoroughly digested in Cushing's[3] monograph. But we are not at the moment so much concerned with the final cause of ulcer. Our interest is rather in trying to show that as total organisms the peptic ulcer susceptible person and the gall-bladder susceptible person are widely different from one another. These differences appear both in the morphologic and physiologic panels. It is possible to show that in each type a high correlation exists between body form, the pattern by which cardiac electropotential develops and disease proclivity. In addition to these findings, however, it appears that a technique which has heretofore been used in the clinic to detect pathologic

changes in function may also be employed to demonstrate special qualities of constitution.

Conclusions. A precision method has been used to study a constitutional character in the physiologic panel.

There is a high degree of constancy over long periods of time in the individual electrocardiographic pattern demonstrated in one or both of: (*a*) an unchanging pathologic state (Einthoven); and (*b*) the circumstance of a continually normal heart.

Significant differences between the electrocardiographic curve patterns for ulcer and gall-bladder people appear to exist within certain age groups.

These differences are also significantly distinct from the electrocardiograms of individuals with normal records selected from a general hospital population.

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ACTION OF THE DIAPHRAGM IN COUGH.

EXPERIMENTAL AND CLINICAL STUDY ON THE HUMAN.*

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THE action of the diaphragm in cough, sneezing, singing, laughing and similar "expiratory phenomena," has never been clearly determined. This problem has become of more clinical importance since phrenicectomy has been applied routinely in the treatment of pulmonary tuberculosis. Thus its solution has acquired considerable practical significance.

Recent experimental and clinical investigations have modified the ideas of the clinician on cough. Cough is no longer the troublesome and annoying symptom requiring alleviation, but a phenomenon which plays an important part in the pathogenesis and the course of pulmonary diseases and when skillfully directed may be of

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great help in their treatment. Bronchial retention and obstruction, which thus far have been given insufficient consideration, are now known to be the principal factors in the pathogenesis of various morbid syndromes of the lung. In atelectasis, postoperative and medical pneumonia, abscess of the lung, bronchiectasis and other pathologic states, bronchial obstruction plays an important rôle in the production and the course of the disease. In fact, when the patency of the bronchi is hampered or suppressed, the part of the lung dependent upon the obstructed bronchus is not only functionally suppressed, but also the fate of its parenchyma will depend upon the nature and the toxicity of microörganisms which may be present in the obstructing agent. While sterile foreign bodies produce, as a rule, uncomplicated atelectasis, septic material coming from the upper respiratory ways may cause suppurative pneumonitis, gangrene or putrid abscess of the lung. Obstruction of a lobar bronchus by viscid and tenacious pneumococcic bronchial exudate may cause, according to the virulence of pneumococcus present in it, benign pneumococcic atelectasis or toxic pneumonia, postoperative or medical.[7a,8b,c]

The serious effects of defective bronchial drainage are especially appreciated by the surgeon and more particularly by the thoracic surgeon. We all have learned to dread this complication in patients with pulmonary suppurations. In thoracoplasties for pulmonary tuberculosis or lobectomies for bronchiectasis, bronchial retention represents the most important single factor in the pathogenesis of all postoperative hemo-respiratory and toxic complications.[7b] Many such patients have been saved from impending asphyxial death by immediate bronchial aspiration and many patients with pulmonary tuberculosis or putrid abscesses have died because of unrecognized retention in the bronchi of the infected exudate. The term "septic bronchial embolism," coined by Ameuille,[1] gives an accurate idea of the pathogenesis of these complications.

Against bronchial retention and obstruction the lung utilizes several and powerful means of defense; this organ, like the intestine, being especially exposed to infection, requires perfect drainage. Of these means of defense, cough is the most important; it is the "watch dog" of the lung as Jackson has put it.[12] Its suppression paralyzes the whole system of defense, since the full action of the ciliary epithelium and of the peristaltic movements of the bronchi are greatly handicapped or suppressed.

Charts of patients with acute or chronic pulmonary infections in which temperatures and amounts of sputum are recorded are most instructive; when cough is hampered and the amount of expectoration decreases, temperature rises and toxicity increases. Conversely, when cough and expectoration are reëstablished, temperature drops and the condition rapidly improves.[7b] It is well known that a few coughing spells usually clear up all symptoms of postoperative

atelectasis and have prevented many asphyxias following hemoptysis in tuberculous patients.

These new conceptions have increased the need of more positive knowledge on the action of the diaphragm in cough. Thus far, no satisfactory solution of this problem has been presented either by physiologists or clinicians. The confusion prevailing in our concept on this subject was clearly shown in an editorial comment[9] on diaphragm in cough: "In all acts of expulsion, coughing, sneezing, laughing, vomiting and crying the diaphragm adds force to the expulsive effort." A reader, Dr. W. D. Zoethout,[10] surprised by this statement, addressed a letter to the editor asking him if he would "kindly explain how the musculature of the diaphragm can contribute power to expiratory efforts."[10] The editor, in his answer, reversed his previous statement and wrote: "There is at present no evidence that the diaphragm adds power to these processes (coughing, sneezing, laughing, crying), which are expiratory acts, or that it favors the expulsion of air out of the lungs. . . ."

Going over the clinical papers related to phrenic interruption in the human, we find the same quandary. A number of authors believe that paralysis of the diaphragm "renders expulsion of sputum easier," others that it "decreases expectoration," and others that "it is without any noticeable effect upon cough and expectoration." An excellent analysis of these conflicting opinions was presented by Carlson, Ballon, Wilson and Graham.[4] Thus Wall[17] attributed the improvement occasionally following phrenicectomy for bronchiectasis to "the greater ease of expectoration which prevents stagnation and decomposition of the exudate in the dilated bronchial tubes." Straub believed that expectoration was facilitated after phrenicectomy because of "the greater compression exerted upon the lungs by the contraction of the abdominal muscles with the diaphragm flaccid." On the contrary, Cooper[6] found that cough was decreased in 40% of these cases. Chernyk[5] came to the conclusion that the effect of phrenicectomy upon cough and expectoration in pulmonary tuberculosis was either favorable or unfavorable, regardless of whether the lesion was located in the base or the apex. The same opinion was expressed by Moore.[14] Wilson,[18] in 21 cases of pulmonary tuberculosis, found that after phrenicectomy expectoration was easier in 5, more difficult in 3 and remained unchanged in 12. Likewise in 18 cases of bronchiectasis, expectoration was made easier in 4, more difficult in 3 and remained unchanged in 11. Berry,[3] in his paper on the results of phrenicectomy, concluded that "in numerous cases paralysis of the diaphragm so hindered cough and drainage that the secretions puddled in the lung and extensive pneumonia developed."

Experimental investigation on animals upon the effects of diaphragmatic paralysis on cough has also led to conflicting conclusions. Lemon[13] and Coryllos and Birnbaum[8a] have noticed no

changes in the respiratory capacity of the dog following phrenicectomy, unilateral or even bilateral. Fine and Starr,[11] in a recent paper, concluded that, in the dog, "paralysis of the diaphragm affords neither help nor hindrance to the force of the expiratory blast, . . . If cough is somewhat less efficient it must be related to other factors such as less inspiratory expansion of the lungs with consequent decrease in the air available for the expiratory blast."

On the contrary, Carlson[4] and his collaborators, have found that lipiodol or foreign bodies (birdshot) introduced into the bronchi of the dog were eliminated more rapidly from the lung with healthy diaphragm than from the lung with paralyzed diaphragm. In one of their experiments, lipiodol was emptied from the lung of the side of the intact diaphragm within 14 days, whereas it remained 59 days in the lung with the paralyzed diaphragm; following phrenicectomy of the intact side, on the same animal, lipiodol was still present in both lungs 30 days later, when the animal died. They concluded that the elimination of lipiodol and foreign bodies is retarded after paralysis of the diaphragm and that at any rate no evidence was found to support the contention that cough and expectoration are facilitated by interruption of the phrenic nerve.

This short review of clinical and experimental data shows that our present knowledge on the action of the diaphragm in cough and expectoration is very limited; we are even in doubt whether there is any such action. Because of these discrepancies, we decided to investigate further this interesting problem.

It soon, however, became clear to us that no progress could be made without more precise knowledge of the mechanics of cough: for if cough really were a purely expiratory phenomenon, the diaphragm, being a strictly inspiratory muscle, should not have any action upon it. But, is cough an exclusively expiratory act? There are in the literature a few statements which were apparently made casually without any particular importance attached. Carlson *et al.*[4] said (loc. cit., p. 575): "As each cough is usually preceded or followed by a deep inspiration and as the diaphragm is an important muscle of inspiration it is probable that in a succession of coughs the excursion of the diaphragm will in some measure condition the efficiency of cough. . . ." On the other hand, Archibald and Brown[2] wrote in their experimental study of cough: "The contraction of the abdominal muscles increases the abdominal pressure which is transmitted through the *semirigid diaphragm* into the thoracic cage," and "while the intercostal muscles tend to elongate the bony framework of the thorax and thus decrease its capacity, the accompanying *contraction and fixation* of the diaphragm further narrow the chest cavity. . . ."

These two ideas of "conditioning of cough," and of possible "contraction of the diaphragm during cough" were the starting points of this work. They furnished a working hypothesis and

aroused doubt as to the solidity of the conception that cough was a strictly expiratory act. In fact, as our work progressed, we were forced to reject this generally accepted opinion. We gradually came to formulate a new theory which seems more in agreement with clinical and experimental data; and throws, we believe, a new light on the relation of diaphragm to cough.

Mechanics of Cough. Our study was based upon the fact that in the presence of a moderate pneumothorax without fluid and with normal parietal and visceral pleuræ, any changes occurring in the intrapulmonary pressures are integrally transmitted to the pleural air, since variations of intrapulmonary pressures occurring during cough are due to the changes of the capacity of the thorax. It is obvious that they must be registered accurately in the graph recorded by a manometer connected with the pleural cavity.

The great number of patients with pneumothorax and phrenicectomy treated in our services offered us the opportunity of comparative studies of intrapleural pressures during cough with intact and with paralyzed diaphragm on the human. Furthermore, patients having bilateral pneumothorax and unilateral paralysis of the diaphragm rendered possible the study of the action of the diaphragm in cough with and without paralysis of the diaphragm on the same patient. We are indebted to our patients for their kind coöperation in this investigation.

Technique. With all usual aseptic precautions, and at the time of a refill for pneumothorax, the needle introduced into the pleural cavity was connected, by means of an aseptic rubber tube, with a recording chloroform manometer. This worked better than the water manometer and gave satisfactory excursions for our records.

This mode of investigation offered a number of marked advantages. It not only permitted the recording of fine changes of pressures occurring during cough in the human, but it also rendered possible the avoidance of errors inherent in experimentation on animals, especially the dog. In fact, if animals are studied, they should be anesthetized and cough produced by artificial stimulation of the larynx. Moreover, the mediastinum of the dog, represented by a flimsy membrane readily permeable to gases, cannot be compared to the thick and more resistant human mediastinum. Furthermore, the horizontal position in which the animal should remain during the experiment does influence the action of the heavy abdominal viscera upon the diaphragm.

Another point of importance is that in the human, the strength, rhythm and frequency of cough can be made to vary at will, thus allowing investigation of this phenomenon in all its details. Last but not least, this procedure renders possible the study of cough in its relations to pathologic conditions of the lung, of the pleura and of the chest walls, which is impossible in animals. Study of cough in consolidation of the lung, bronchial stenosis or obstruction,

fibrotic or atelectatic retraction of the lung, in decreased pulmonary expansion due to thickened visceral pleura, in rigid mediastinum, in the presence of fluid in the pleural cavity and in reduced mobility of the chest walls following thoracoplasty or excessive inflammatory thickening of the parietal pleura, are of considerable interest.

It is not our intention to enter here into these details which will be reported later. We shall limit this study to the mechanics of cough in cases with normal or almost normal lungs, pleura and chest wall.

Our Concept. We regard cough as far from a simple expiratory phenomenon. It really is composed of three distinct phases, inspiratory, compressive and expulsive, each of which presents special mechanical and physiologic characteristics. Cough is represented by the integration of these three phases; none of them can be omitted when we consider cough, without exposure to misinterpretations and erroneous conclusions. In other words, cough should be considered as a whole; it is a reflex phenomenon which can be started and stopped voluntarily. However, once started, and if not interfered with, it proceeds according to a fixed pattern, just as do deglutition, vomiting and defecation.

Cough is composed of a deep inspiration followed by a strong expiration. However, the expiratory act is in reality composed of two different phases: one, short, during which the glottis remains closed and strong positive pressure is built up in the lungs; the second is longer, begins with the opening of the glottis and ends with the sustained expulsion of the compressed air.

Thus cough is composed of three distinct phases: "Inspiratory," "compressive" and "expulsive." These three phases can be likened to the three phases of the deflagration of a gun; the inspiratory to the loading of the gun, the compressive phase to the deflagration of powder and production of gases under pressure, and the expulsive phase to the ejection of the bullet from the barrel of the gun.

This partition of cough into three phases facilitates the study of the action of the diaphragm separately in each.

1. *Inspiratory Phase.* During the inspiratory phase, the action of the diaphragm is evident. It is also obvious that the amount of air loaded into the corresponding lung depends upon the condition of the diaphragm. When this muscle is paralyzed it cannot contract and therefore the vertical diameter of the chest is not increased. Hence, the capacity of the hemithorax corresponding to the paralyzed diaphragm increases less than that of the other side. Furthermore, as after phrenicectomy the diaphragm loses its tonus and elasticity and is changed to a flimsy membrane, it is drawn upward during inspiratory increase of the intrapleural negative pressure. It should be noted, however, that because of the normal contraction of the healthy diaphragm the inspiratory negative pressure is greater in the healthy side; therefore the mediastinum

is displaced towards this side and thus the difference between the pressures of the two hemithoraces tends to decrease. Nevertheless, complete equilibrium can be reached only in animals with an extremely mobile mediastinum, such as the dog. Therefore with the hemiparalyzed diaphragm of man the amount of air is smaller and the expiratory blast of air during the third phase less strong.

Much more than by hemiparalysis is the inspiratory phase of cough influenced by any cause which impairs the ability of the lung to expand; bronchial obstruction of any kind, the presence of large amounts of fluid in the pleural cavity, thickening of the parietal and visceral pleuræ or immobilization of the chest wall to expand (chronic empyema, thoracoplasty)—all these diminish considerably the efficiency of this phase of cough.

2. *Compressive Phase.* During the second or compressive phase the action of the diaphragm is of the greatest interest. In fact, high positive pressures cannot be built up in the chest unless its walls have acquired a rigidity proportionate to these pressures. Therefore, the rigidity must be considerable since the positive pressures reach 80 and even 100 mm. Hg.

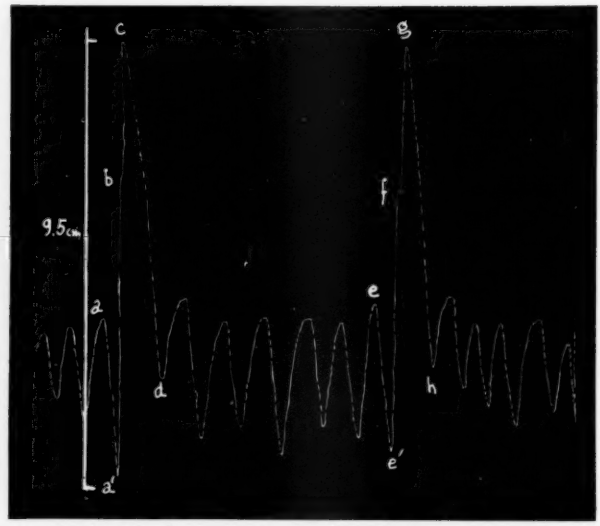
Let us follow this phase closely. Under the action of the expiratory muscles, the most important of which are the abdominal muscles, the ribs and sternum are drawn downwards causing a marked reduction of the capacity of the chest and pressure upon the air which is entrapped into the lung by the closure of the glottis. It should always be remembered that positive pressures in the chest are due to the centripetal compression exerted upon the inflated lungs by the retracting chest walls and the compressed abdominal viscera.

It is easy to understand the mechanism by which the rigidity of the thoracic walls is insured. The bony skeleton of its walls, complemented by the contracting intercostal muscles, can easily transform the thorax into a rigid cage. But there are the upper and the lower openings of the chest. The superior opening is small and the apical pleuræ which obturate it superiorly are solidly reinforced by numerous fibrotic bands; in the center we find an extrapleural space occupied by the organs passing from the neck into the chest.

It is more difficult to understand the mechanism by which the soft and easily yielding diaphragm, representing the bottom of the thoracic cage, acquires the considerable rigidity necessary to resist such enormous positive pressures as 80 to 100 mm. Hg, or even more. Three hypotheses are possible.

A. That the propulsion of the abdominal viscera upwards under the action of the contracting abdominal muscles is checked by the tonus and the elasticity of the diaphragm. But this cannot be true, because then the diaphragm should be strained to its breaking point and should not rise further into the chest in each successive cough movement.

B. The push of the abdominal viscera comes to an equilibrium with the increased intrathoracic pressure. Thus the subsequent rising of the diaphragm with each cough could be explained by the decreased intrathoracic pressure following each short opening of the glottis. But if this were so, why does the paralyzed diaphragm rise into the chest far above the healthy one; moreover why, at each opening of the glottis, does it jump much higher than the non-paralyzed one? In fact, when we follow in the fluoroscope the movements of the diaphragm of a patient with the diaphragm



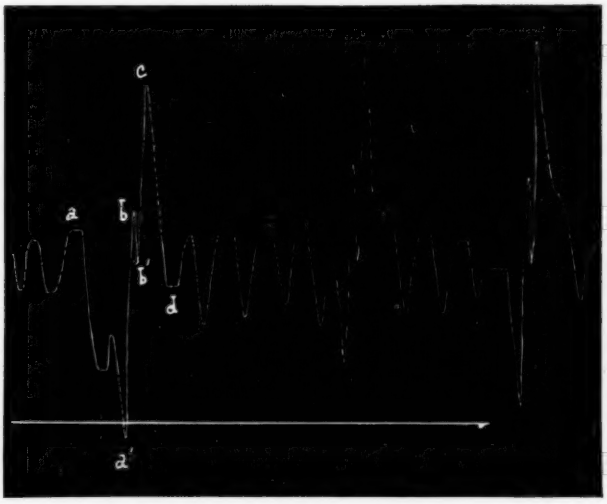
GRAPH 1.—Patient T. G., aged 23, female, pulmonary tuberculosis. Pneumothorax. Diaphragms intact. Graphs of two cough movements without inspiratory interruption, inspiration downstroke.

paralyzed on one side, while the patient is instructed to make short successive coughs without inspiratory movement between them, we see very clearly that the healthy diaphragm rises a little more with each cough, whereas the paralyzed diaphragm "jumps" high and falls again. We must admit, therefore, that something holds down the viscera during the opening of the glottis and that this cannot be the tonus alone of the diaphragm. The unquestionable conclusion is that the diaphragm does contract during the compressive phase of cough.

C. The third hypothesis is that the diaphragm contracts during the compressive and the expulsive phases of cough. Thus the diaphragm checks the rise of the viscera into the chest and renders rigid the bottom of the thoracic cavity. It will be shown that this concept offers an easy explanation of other puzzling questions concerning the expulsive phase of cough.

These differences in the movements of the healthy and paralyzed diaphragms are clearly shown in our graphs. We give here two of them. These graphs were obtained by a recording chloroform manometer connected by a rubber tube to the usual pneumothorax needle introduced into pleural cavities with healthy (Graph 1) and with paralyzed diaphragm (Graph 2).

Following are clinical notes of the 2 patients who furnished these graphs and who were selected as nearly similar as possible.



GRAPH 2.—Patient F. L., aged 22, female. Pulmonary tuberculosis. Right pneumothorax and previous avulsion of the right phrenic nerve. Right diaphragm paralyzed, inspiration downstroke.

CASE 1.—T. G., aged 23, female, Puerto Rican; bilateral pulmonary tuberculosis; had had bilateral pneumothorax, completed by bilateral pneumonolysis. Both upper lobes were selectively collapsed while the lower lobes of both lungs were allowed to reëxpand. The vital capacity was 1200 cc. The phrenic nerves were intact and the function of the diaphragm was normal.

CASE 2.—F. L., aged 22, white, had a pneumothorax in one side. A complete avulsion of the phrenic nerve (30 cm.) had been performed previously. Pneumonolysis was performed for section of apical adhesions which had opposed a selective collapse of the apex. Actually the upper lobe was selectively collapsed while the lower lobe was allowed to reëxpand. Vital capacity, 1400 cc.

Since all other conditions in these patients were identical, it seems reasonable to assume that all differences shown in the two records should be ascribed to the paralysis of the diaphragm.

These patients were instructed to cough twice in succession without inspiratory interruption, so that each graph would represent two movements of cough without intervening inspiration.

For reasons developed previously, it can be accepted that the changes in pressures in the pleura faithfully translate corresponding changes of pressures in the lung, so that in the last analysis it makes no difference whether the graphs were taken from the pleura or directly from the lung—the latter being impossible in the human. A study of the two graphs shows that they differ in all three phases but more especially in the compressive and expulsive ones.

In Graph 1, the inspiratory phase (*aa'*) is represented by a clean-cut downstroke, about three times longer than the downstroke of the normal quiet inspiration. It is accomplished in two movements (*aa'*); it is possible that the first downstroke is due to the expansion of the chest and the second to the contraction of the healthy diaphragm of the other side, causing as was said above, displacement of the mediastinum towards the healthy side. Moreover it has been repeatedly, although not constantly, noted that the inspiratory movement preceding cough starts a trifle earlier in the thorax with paralyzed diaphragm than on the healthy side.

The upstroke *a'bc* presents the compressive phase of two successive cough movements *a'b* in the first and *Cc* in the second. *C* marks (Graph 1) the short period between the two coughs during which the glottis was opened. It is clearly shown that this short and partial release of pressure affects very little the intrapleural and intrapulmonary pressures on the side with healthy diaphragm.

In Graph 2 we find that the two cough movements *a'b* and *b'c* are separated by a downstroke *bb'*; this indicates either that during the short opening of the glottis a more marked drop of pressure occurred on this side or that the push of the viscera upwards at the end of the first cough was not checked as in Case 1. Obviously, a more marked drop of intrapleural (and intrapulmonary) pressures on the side of the paralyzed diaphragm is not admissible because this drop, due to the opening of the glottis, is independent of the condition of the diaphragm.

3. *Expulsive Phase. In the third, or expulsive, phase of cough*, this checking action of the diaphragm becomes more apparent. If we inspect the abdomen of a man during cough, we see that in each coughing effort a movement of retraction of the abdominal wall takes place. When a subject is instructed to perform successive movements of cough without inspiratory interruption, we see successive contractions of the abdominal walls so that they retract each time a little more than in the preceding movement. When a subject with healthy diaphragm is examined fluoroscopically while coughing, the diaphragm is seen to assume a little more elevated position with each cough. It seems to restrain the abdominal viscera from jumping upwards into the chest cavity, as occurs when the diaphragm is paralyzed. This is particularly noticeable when a subject makes strong successive cough movements in an endeavor to expel tenacious sputum. In each movement the diaphragm rises a little more,

as if it were regulating the expulsion of air in an effort to prevent waste of time, air and energy. Likewise, the diaphragm acting as an antagonist to the abdominal muscles, regulates the strength and length of cough to the needs, that is, to the resistance opposed by foreign bodies present in the bronchial tree. There is no doubt that this adjustment is necessary and does take place. We do not cough with the same strength when we strive to dislodge tenacious sputum or a foreign body stuck to the bronchi as when we gently push a small quantity of phlegm from the upper respiratory ways.

At the same time, by its synchronous contraction with the abdominal muscles, the diaphragm insures the rigidity of the floor of the thorax during the compressive and expulsive phases of cough. This is a prerequisite condition because of the tremendous positive pressures necessary for the production of the strong draft of air needed for the expulsion of foreign matter from the bronchial tree. Rohrer[15] has calculated the velocity of air during cough as it passes through the various segments of the human respiratory tract. He found that it varied from 0.5 to 2 meters per second in the respiratory bronchioli and from 50 to 120 meters (150 to 360 feet) per second in the glottis. These latter velocities are comparable to wind velocities of severe storms. Calculated at 300 feet per second, the speed of air in the glottis is equal to 20 miles an hour, which compares very favorably with the 30 mile per hour wind speed of strong hurricanes.

Comment. The facts thus far shown in this study seem to prove that the diaphragm contracts during the three phases of cough. If this contention is accepted, the explanation of all difficult points on cough become simple.

The rigidity of the floor of the chest, unaccounted for in other theories, a condition necessary for the development of high positive pressures in the lungs during the compressive period of cough, is easily explained. The pushing upwards of the abdominal viscera against the downward pushing of the contracting diaphragm insures the rigidity of the bottom of the thorax in the same way as the simultaneous contraction of flexor and extensor muscles of the arm and forearm insures the rigidity of the elbow. In fact, this is the usual mechanism by which rigidity is obtained in any part of the body.

Thus, the diaphragm here acts as a muscle antagonist to the abdominal and other expiratory muscles. This conclusion is, I believe, the most important point and gives us the key to the whole problem of the action of the diaphragm in cough. It is a simple physiologic law that wherever in the organism a movement is accomplished either by the skeletal or visceral muscles, it is always performed by the co-action of two antagonist muscular systems—one acting as a brake upon the other. It is by this mechanism that movements can be adjusted to the needs with accuracy and without waste of

time and energy. We know that the accuracy and speed of movements of the fingers is hampered when the integrity of either their flexor or extensor system is disturbed. Likewise the regularity and efficiency of movements of the intestine are disturbed when either their sympathetic or their vagus innervation is involved. This fine co-action of the two antagonist muscular systems is seen also in all tubular organs, such as the esophagus, ureters, and so forth; when a foreign body is present in their lumen, peristaltic contractions of their walls tend to expel the obstructing agent; the strength of these movements is adjusted to the resistance offered by the foreign body.

The same mechanism is repeated in cough. The objective of the reflex is the expulsion of foreign matter lodged in the bronchi; the means to this effect are blasts of air, besides the "tussic squeeze" of Jackson[12]; it is obvious that the strength and rhythm of these blasts must be proportionate to the resistance offered by these agents. Therefore, a regulating mechanism of the blasts of air is necessary in order to adjust their expelling strength without waste of the explosive material—here the compressed air—and of energy, represented here by the action of the muscles activating the bellows. Therefore, the theory of the co-action of two antagonistic motor systems can alone explain the regulating mechanism of cough.

This action of the diaphragm is well seen and easily proven in other expiratory acts, similar to cough but less rapid and less explosive than cough, or sneezing. Such acts are singing and effort; when we observe in the fluoroscope a person while he sings, whistles or emits a continuous sound we can clearly see this regulating action of the diaphragm. Likewise during manual effort, in which the chest is immobilized in inspiration with the glottis closed in order to insure a steady point of insertion for the muscles of the arms and of the abdomen, again the degree of contraction of the diaphragm and of the abdominal muscles are proportionate to the positive pressures which should be built up in the chest in order to insure an immobilization and rigidity of the chest cage proportionate to the effort. We do not find the same intrathoracic pressures when a man tries to lift 50 pounds as when he tries to lift 500 pounds.

Thus the diaphragm, contrary to the theories accepted thus far that "it is without any action in coughing, sneezing, crying, etc.," does take an important part in all expiratory acts such as cough, sneezing, singing, effort, and so forth. However, the diaphragm does not directly help expulsion of air from the lungs. The action of this muscle is *to regulate and adjust the expulsive efficiency of cough.* This action is one more example of the amazing efficiency, accuracy and economy with which the body machine operates.

Conclusions. 1. Review of knowledge of the action of the diaphragm in cough reveals the absence of any acceptable concept on this subject.

2. Clinical and experimental evidence suggest a new conception,

according to which the action of the diaphragm is that of a regulator of the strength of the expulsive force of cough necessary to overcome the resistance of matter lodged in the bronchial tree.

3. Cough is not a simple expiratory act but is composed of three distinct phases, inspiratory, compressive and expulsive.

4. The diaphragm acts as an antagonist muscle to the expiratory muscles and contracts during the three phases of cough; by its co-action with its antagonist expiratory, thoracic and abdominal muscles, it insures the rigidity of the floor of the thoracic cage during its compressive phase and it regulates the efficiency of cough with the greatest saving of time and energy during its expulsive phase. This action of the diaphragm is in accordance with the general physiologic laws of movement in the animal economy.

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CARCINOMA OF THE BRONCHUS IN ASSOCIATION WITH ANTHRACOSILICOSIS.

A Study of Four Cases.

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In a condition such as anthracosilicosis in which chronic irritation of the bronchus and lung by coal and silica is an outstanding feature, a relatively high incidence of primary bronchial and pulmonary carcinoma might be expected. From postmortem findings, however, it has been generally regarded that there is no relationship between pneumonoconiosis and pulmonary new growths. In fact, only a few cases of bronchogenic carcinoma in association with anthracosilicosis are reported.[1,4,5]

Between January, 1934, and December, 1936, 174 cases of anthracosilicosis in various stages, with or without pulmonary tubercu-

losis, were treated at this Sanatorium. Of this number, 36 came to necropsy. Among these, 4 presented primary carcinoma of the bronchus. Briefly, the clinical and pathologic observations on these cases are as follows:

Case Abstracts.—Case 1 (No. 9199). White male, aged 43, anthracite coal miner 9 years, was admitted on March 3, 1934, complaining of dyspnea, hemoptysis, pain in the left chest, cough and expectoration. He had noted dyspnea on exertion 4 months previously, soon followed by persistent dull pain in the left chest. A dry cough developed which later became productive. The sputum was constantly mixed with blood. The family history was negative and there was no past history of influenza. Fig. 1.

Physical Examination. Chest was rounded, expansion and vocal fremitus equal on both sides. There was slight dullness over the left apex but resonance over the rest of the left lung and the entire right lung. The breath sounds were loud over both lungs, including the left apex. No râles. The sputum was negative for tubercle bacilli in 26 specimens.

Roentgen Ray Examination (Fig. 1) showed a homogeneous opacity involving the left upper lobe area with scattered mottling throughout the remainder of the left lung and the entire right lung.

Temperature was normal except on two occasions when it rose to 101° F. Pulse rate varied from 90 to 100, and respiratory rate 25 to 30 per minute.

Dyspnea and cough became worse. The sputum was constantly mixed with large amounts of fresh blood. Pain in the left chest persisted. The patient died May 23, 1934. Fig. 3.

Necropsy. A large tumor encircled the trachea and aorta. The left lung showed a hard tumor occluding the upper lobe bronchus and producing atelectasis of that lobe. In the center of the atelectatic lobe was a large cavity containing necrotic material. Throughout the left lung were scattered small tumor nodules. The hilum lymph nodes showed metastasis.

Microscopic Examination. The tumor consisted of small round and occasionally spindle-shaped cells with dark nuclei and scanty cytoplasm and considerable intercellular stroma. The anthracosilicotic nodules were extensively broken up. Some tumor cells formed glandlike structures. The bronchioles showed desquamation. The lymph channels were filled with tumor cells. Large necrotic areas were common and many of the tumor nodules showed central necrosis. The bronchial cartilages were extensively destroyed by tumor cells. Diagnosis: Carcinoma, undifferentiated type.

Case 2 (No. 9477). White male, aged 48, anthracite coal miner 25 years, was admitted on July 6, 1935, complaining of dyspnea, hemoptysis, pain in the right chest, cough and expectoration. He had noted dyspnea on exertion for 4 months. About the same time he began to feel persistent pain in the right chest. Soon cough set in with expectoration of about 2 oz. of blood-streaked sputum daily. The family history was negative and there was no past history of influenza. Fig. 5.

Physical Examination. Chest was rounded, expansion limited on the right side, with absent fremitus over the right lower chest where the percussion note was flat and the breath sounds were absent. The right upper lobe and the entire left lung were resonant and the breath sounds well heard. A few crackling râles were present over the left base. Heart was displaced to the left side. The sputum was negative for tubercle bacilli in 13 specimens.

Roentgen Ray Examination (Fig. 2) revealed a dense shadow in the right lower chest, suggesting pleural effusion. Throughout the remainder of the right lung and the entire left lung were prominent tissue markings and dis-

Fig. 1.

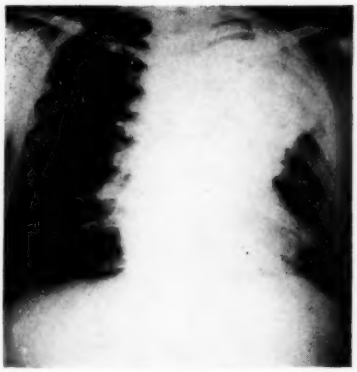


Fig. 2.

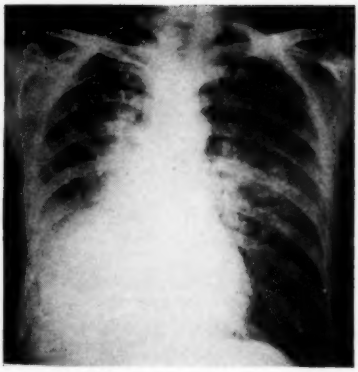
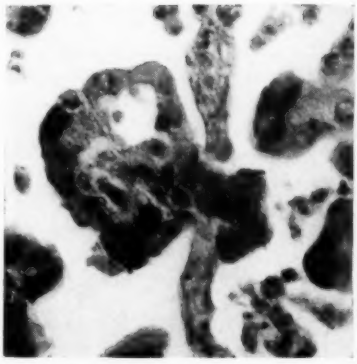


Fig. 3.



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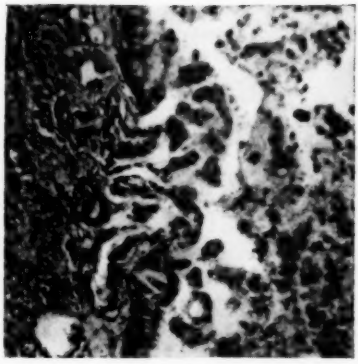

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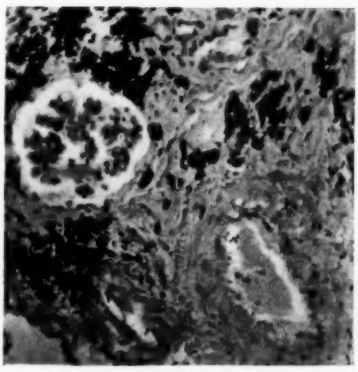


Fig. 6.

Fig. 1.—Atelectasis of left upper lobe due to bronchial obstruction. Nodules in remainder of left lung. Increased tissue markings in right lung.

Fig. 2.—Pleural effusion on the right. Increased tissue markings and disseminated nodules in both lungs.

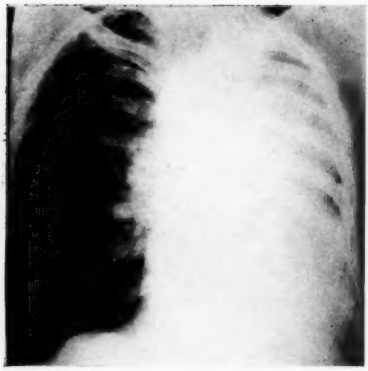
Fig. 3.—Tumor cells passing through an alveolar pore. (× 450.)

Fig. 4.—A tumor rupturing into a bronchus. (× 100.)

Fig. 5.—Perivascular lymph vessels engorged with tumor cells. (× 100.)

Fig. 6.—Tumor cells in an interlobar adhesion. (× 100.)

FIG. 7.



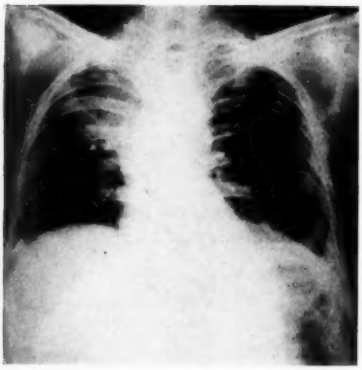
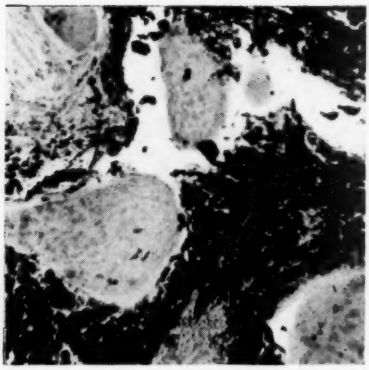


FIG. 9.

FIG. 8.



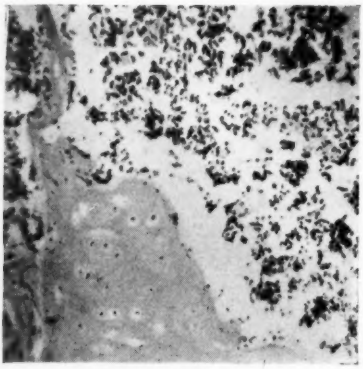


FIG. 10.

FIG. 11.

FIG. 7.—Atelectasis of left lung due to bronchial obstruction. Nodules in right lung.

FIG. 8.—Invasion of anthracosilicotic nodule by tumor cells. (× 100.)

FIG. 9.—Atelectasis of right upper lobe. Increased tissue markings in left lung and remainder of right lung.

FIG. 10.—Destruction of bronchial cartilage by tumor cells. (× 100.)

FIG. 11.—Pulmonary artery in atelectatic right upper lobe has fewer ramifications, and its caliber is narrowed.

seminated small poorly defined nodular shadows, being most numerous in the hilum regions.

Temperature was practically normal. Pulse rate varied from 84 to 100, and respiratory rate between 20 to 35 per minute.

On August 20, 1935, the patient developed a complete left sided hemiplegia and died within an hour.

FIG. 9. *Necropsy.* Directly beneath the visceral pleura of each lung were scattered grayish nodules varying in size from a pin-point to 1 mm. Intermingled with these were anthracosilicotic nodules measuring from 1 mm. to 5 mm. The visceral pleura of the right lung was thickened and covered with fibrinous material. Both kinds of nodules were prominent on section. There was considerable peribronchial and perivascular fibrosis. Some bronchioles were occluded with cell débris. Several small blood-vessels were thrombosed. The liver and kidneys showed grayish nodules of the same character as those in the lungs. Other organs in the abdomen and pelvis were negative.

Microscopic Examination. The grayish nodules were tumors consisting of cylindrical and cuboidal cells having pale nuclei, oval in shape. In many areas the alveolar septa were lined by tumor cells, some of which formed papillary projections into the alveolar spaces, while others were passing through the alveolar pores (Fig. 3). Anthracosilicotic nodules were broken up by tumor cells. The mucosa of the bronchioles showed thinning and areas of desquamation. Small tumors disrupted the bronchial mucosa and discharged the tumor cells into the bronchial lumen (Fig. 4). There was much peribronchial and perivascular fibrosis. The peribronchial and perivascular lymph channels were filled with tumor cells (Fig. 5). Thrombosed blood-vessels were most numerous in the right lower lobe and surrounding them were areas of infarction, some of which showed fibrotic capsules. The pleura over the right lung showed tumor cells covering its surface. The strandlike adhesions between the lower and middle lobes showed tumor cells (Fig. 6). The bronchial cartilages were extensively destroyed by tumor cells. Diagnosis: Cylindrical cell carcinoma.

FIG. 10.

CASE 3 (No. 9534). White male, aged 53, anthracite coal miner 43 years, was admitted on September 20, 1935, complaining of dyspnea, hemoptysis, cough and expectoration. The onset was 1½ years previous to admission when he noticed dyspnea on exertion, which gradually became worse. For the past 20 years he has had slight cough and expectoration which became worse during the last 2 months. Shortly before admission he had hemoptysis and thereafter the sputum was frequently blood-streaked. The family history was negative and there was no past history of influenza.

Physical Examination. Chest was rounded. There was limited expansion on the left with diminished vocal fremitus and dullness over the upper lobe. Over the rest of the left lung and the entire right lung was resonance with loud breath sounds. Heart was displaced to the left. The sputum was negative for tubercle bacilli in 7 specimens.

Roentgen Ray Examination (Fig. 7) showed numerous independent nodular shadows throughout the right lung. On the left was even density with displacement of the heart to that side.

Temperature was normal. Pulse rate was from 80 to 100, and respiratory rate from 25 to 35 per minute.

Following admission, dyspnea, cough and expectoration became worse and the patient died on October 6, 1935.

Necropsy. Both lungs showed scattered anthracosilicotic nodules measuring from 1 mm. to 5 mm. The left upper lobe was atelectatic due to an occlusion of its bronchus by a tumor. Within the center of the atelectatic lobe were four cavities containing necrotic material. The left lower lobe presented an appearance of gray hepatization. There was much peri-

bronchial and perivascular fibrosis in both lungs. Some blood-vessels were thrombosed.

Microscopic Examination. The tumor consisted of squamous cells showing pearl formation. Many tumor nodules showed necrotic centers. The lymph vessels contained tumor cells in large numbers. The blood-vessels were sclerotic with a great deal of perivascular fibrosis and some were thrombosed. Adjacent to the thrombotic vessels were areas of infarction, some of which had undergone necrosis. Some infarcts had fibrous capsules. Anthracosilicotic nodules were numerous and many of them were extensively broken up by tumor cells (Fig. 8). In the left lung, the alveolar septa were greatly thickened by increase of the connective tissue and cellular infiltration. The alveoli were filled with fibrinous material containing tumor cells. Shreds of fibrin passed through the alveolar pores. The mucosa of the bronchioles showed thinning and areas of desquamation. Peribronchial fibrosis was common. The bronchial cartilages in the left lung were extensively destroyed by tumor cells. Diagnosis: Squamous cell carcinoma.

Case 4 (No. 9816). White male, aged 36, anthracite coal miner 20 years, was admitted on December 19, 1936, complaining of dyspnea, hemoptysis, cough, expectoration and fullness in the epigastrium. Dyspnea set in a year ago. During the last 6 months the patient had fullness in the epigastrium with some cough, expectoration and occasional hemoptysis. The family history was negative and there was no past history of influenza.

Physical Examination. Chest was rounded. Expansion was fairly good on both sides with normal vocal fremitus. Over the right upper lobe was dullness but the breath sounds were easily heard. Over the remainder of the right lung and the entire left lung the percussion note was resonant and the breath sounds were loud and well heard. No râles. Heart was displaced to the right. Liver was enlarged and nodular. The sputum was negative for tubercle bacilli.

Roentgen Ray Examination (Fig. 9) showed haziness in the right upper lobe region. Throughout the remainder of the right lung and the entire left lung were increased tissue markings. The trachea and the heart were displaced towards the right.

Temperature was normal. Pulse rate was from 80 to 90, and respiratory rate from 25 to 35 per minute.

The patient died on December 27, 1936.

Necropsy. Both lungs showed scattered anthracosilicotic nodules measuring from 1 mm. to 4 mm. The right upper lobe was atelectatic due to a hard tumor constricting the lumen of its bronchus. Within the center of the atelectatic lobe was a large cavity containing blood-tinged necrotic material. The lower lobe of each lung showed scattered tumor nodules. There was considerable peribronchial and perivascular fibrosis. Some of the blood-vessels were thrombosed.

Microscopic Examination. The tumor consisted of small round cells with very scanty cytoplasm densely packed and very little intercellular stroma. Some cells formed glandlike structures. The bronchial cartilages were extensively destroyed by tumor cells (Fig. 10). There was peribronchial and perivascular fibrosis. The lymph vessels were filled with tumor cells. Some blood-vessels showed thrombi containing tumor cells. Adjacent to the thrombotic vessels were areas of infarction, some of which had undergone necrosis. The anthracosilicotic nodules were broken up by tumor cells. Diagnosis: Carcinoma, undifferentiated type.

Discussion. The outstanding clinical features in these cases were dyspnea, hemoptysis, cough, expectoration and pain in the chest. These symptoms, except for hemoptysis, are the usual manifestations

in long standing anthracosilicosis. Though hemoptysis may occur in association with pulmonary tuberculosis, in pure anthracosilicosis it is rare. Due to the absence of any unusual clinical findings but only those complaints commonly encountered in anthracosilicosis complicated by pulmonary tuberculosis, these cases were regarded as anthracosilicosis with pulmonary tuberculosis, until suspicion was aroused by the repeatedly negative sputum examinations. The sputum may be repeatedly negative for tubercle bacilli in anthracosilicosis with pulmonary tuberculosis, but in cases in which hemoptysis occurs tubercle bacilli are usually found. The negative sputum for tubercle bacilli in anthracosilicosis with hemoptysis a frequent symptom, should arouse suspicion for malignant disease of the bronchus.

Dyspnea was the earliest and most prominent symptom in every case partly due to preëxistent anthracosilicosis with concomitant emphysema. In all the cases there was widespread destruction of the bronchial cartilages. The tumor cells in the peribronchial lymphatics penetrated through the vessel walls and invaded the bronchial cartilages. In some areas the bronchioles appeared collapsed due to destruction of the cartilages and one may surmise that in such a case the ingress and egress of air must have been seriously interfered with.

Although there was extensive cavitation with retention of necrotic matter in Cases 1, 3 and 4, the common symptoms of pulmonary abscess, such as fever and chill, were lacking. This could be due to slow absorption of the toxic material on account of an impairment of the lymphatic circulation resulting from anthracosilicosis. Furthermore, a Roentgen ray examination of the pulmonary artery in Case 4 (Fig. 11) shows a distinct decrease in the number and caliber of its ramifications in the atelectatic right upper lobe, within the center of which was a large cavity containing necrotic matter. One may assume that the circulation in this lobe was impaired, and was capable of absorbing only a small amount of the toxic substance.

Farrell[2] stated that the most constant Roentgen ray finding in bronchial carcinoma is evidence of collapse of the lung in part or as a whole and the least characteristic of the frequently encountered changes secondary to bronchial new growths is an increase in the linear markings. These markings, he observed, were often looked upon as due to some non-specific inflammation; though, when it occurred in the upper portions of the lung fields, it was often diagnosed as tuberculosis and in the lower as bronchiectasis. In Cases 1, 3 and 4, the Roentgen ray appearance was characteristic of pulmonary atelectasis due to a bronchial occlusion. Case 2 lacked the usual Roentgen ray signs of bronchial carcinoma. The dense opacity in the right lower lobe area was due to pleural effusion. The exaggerated linear shadows in the lungs resulted from peribronchial

and perivascular fibrosis, and invasion of the lymph channels by tumor cells. The scattered small nodular shadows throughout the lungs, particularly about the hilum regions were due to the anthracosilicotic and tumor nodules. On account of tumor cells surrounding them, the anthracosilicotic nodules lacked the usually sharp outlines.

The principal histopathologic feature in these cases was the extensiveness of destruction of the anthracosilicotic nodules by the tumor cells. Some of the anthracotic nodules consisted of collapsed alveoli, the walls of which contained much pigment. They were easily pushed apart by tumor cells filling the alveolar spaces. In the center of some of the anthracosilicotic nodules were small lymph vessels filled with tumor cells. Some cells broke through the walls of the lymph vessels and invaded the anthracosilicotic nodules. The acellular central portions of the silicotic nodules were free of tumor cells, but their cellular peripheral zones were thickly crowded with them. In spite of fibrosis the perivascular and peribronchial lymphatics were capable of tremendous dilatation and engorgement by tumor cells.

In Cases 2 and 3, small tumors disrupted the bronchial mucosa and discharged tumor cells into the bronchial lumen. The mucous material in the bronchi became loaded with tumor cells. Entrance of mucus containing tumor cells into the non-involved parts of the lung appeared to be an important metastatic factor. Tumor cells passing through the alveolar pores were observed. Unquestionably, the lymphatics played an important rôle in intrapulmonary metastasis in these cases. In Case 2, a sagittal section of a thin thread-like adhesion between the middle and lower lobes showed that the tumor cells from the surface of the visceral pleura covering the lower lobe had entered the adhesion. Many blood-vessels in all the cases showed thrombi containing tumor cells.

The cavities in the atelectatic lobes must have resulted from evacuation of the abscesses resulting from an interference with the normal bronchial drainage. Small areas of necrosis were observed in all the cases and they seemed to have resulted from pulmonary infarction caused by tumor cells occluding the blood-vessels. The areas of infarction were most numerous in the right lower lobe of Case 2 and the left lower lobe of Case 3. Many tumor nodules showed central necrosis.

According to Fischer-Wasels[3] cancer develops when the germ plasm having cancer tendency is irritated by such factors as tobacco smoke, tar, dust, acute or chronic disease. Unquestionably, the bronchial mucosa and the pulmonary tissues in these cases were irritated by the particles of coal and silica over a long period of time. Such chronic irritation might well have had some influence on the development of carcinoma in these cases.

Summary and Conclusion. 1. Clinical and pathologic observations on 4 cases of primary carcinoma of the bronchus associated with anthracosilicosis are briefly described.

2. Dyspnea, hemoptysis, cough, expectoration and pain in the chest were the outstanding symptoms. Sputum negative for tubercle bacilli (with hemoptysis a frequent symptom) excited a suspicion of primary malignant growth of the bronchus.

3. Roentgen ray diagnosis of diffuse bronchogenic carcinomatosis is difficult when anthracosilicosis coëxists.

4. Extensive destruction of the bronchial cartilages, resulting in collapse of the involved bronchi, might have been responsible for severity of dyspnea.

5. Capability of the peribronchial and perivascular lymphatics to dilate in spite of fibrosis surrounding them was noted.

6. Spread of tumor cells through the alveolar pores and interlobar adhesions was observed.

7. Absence of toxic symptoms of pulmonary suppuration was attributed to impaired lymphatic absorption and lessened blood flow through the atelectatic lungs.

8. A suggestion is made that in these cases anthracosilicosis might have had an indirect influence on development of carcinoma of the bronchus.

The writer desires to tender his thanks to Dr. Frank A. Craig for his permission to use the Sanatorium material and to Dr. Joseph Walsh for his valuable criticisms and permission to use the necropsy specimens.

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MASTITIS IN THE MALE.

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Of all swellings of the male breast, that produced by an acute or chronic mastitis is the most frequent. Tumors of the male breast do not differ essentially from those seen of the female, except as modified by the anatomy of a non-functioning rudimentary organ.

Of all tumors of the mammary gland only approximately 1% occurs in males. Since chronic irritation in the mammary glands of females frequently is followed by malignant changes, it might be expected that the mammary glands of males also would show malignant changes frequently. Such, however, is not the case, as is apparent by an examination of the rather extensive literature upon the subject. The earlier literature seems to indicate that a large per-

centage of swellings of the mammary gland in males is malignant, benign conditions being rarely seen. Reports of the past few years give an entirely opposite view. The occurrence of malignant tumors in the male is relatively uncommon.

This report is based upon a study of 25,689 patients admitted to a single institution during a recent 5-year period. In only 1 instance was a malignancy of the breast found. During the same period 16 males were found with benign swellings of the breast.

The differentiation between decidedly malignant tumors of the breast and a chronic mastitis is not difficult; but benign and very early malignant lesions are often very difficult to distinguish and especially where chronic inflammation has existed for some time. Not only may chronic productive mastitis result in overgrowth of epithelium and connective tissue, which may gradually pass into malignant manifestations, but senile involution may also be accompanied by irregular production of epithelium and stroma (Ewing[5]).

Cheatle[2b] emphasizes the occurrence of desquamation of the proliferated epithelial cells within the ducts and acini, and often papillary overgrowth. The atypical proliferation that may follow, with some cells exhibiting signs of malignancy, he considers a precancerous state.

The history of mammary malignancies is usually that a chronic inflammatory process preceded the malignancy, and that the development of the tumor was slow and insidious. Since malignant tumors appear frequently to arise on chronic mastitis, removal of such a minor condition seems definitely justified.

The normal anatomy of the male breast has received far less careful study than has that of the female breast. Most textbooks devote little space to a description of a normal male mammary gland, usually being satisfied with the statement that it contains only rudiments of gland structures. Andrews and Kampmeier[1] have shown, however, by careful dissection that in every male breast there is a complicated system of ducts and alveoli and "that in adult males the breast tissue persists in essentially the same state as the pre-adolescent female." The ducts and alveoli are lined by a single layer of columnar epithelium and the ducts are invariably patent. The glandular structure is sharply limited from the connective tissue by a limiting membrane. The fibrous areas about the ducts often resembles proliferating fibrous tissue.

There are two important predisposing etiologic factors in mastitis of males. Trauma, a single injury, or continued irritation such as the rubbing of a mail pouch across the nipple was apparently an etiologic factor in 2 of the cases presented here. The second factor is a dirty skin, one that harbors pyogenic bacteria in large numbers, which when rubbed into a traumatized glandular structure find a suitable soil for growth. There is no evidence that infection is hematogenous although such a source is not impossible. The

presence of infection elsewhere adds to the chances of infection of the skin in the region of the breast and subsequent involvement of the ducts. Two patients in this series gave a history of a single severe trauma. Two others, letter carriers, attributed the condition to irritation by the strap of the mail sack. The remainder gave no history of injury. All were working men of apparently uncleanly habits. Six were machinists exposed to much heat and dirt. It is not surprising that acute and chronic infection develops in such a complicated glandular structure with ducts open to receive infection and with stagnation of the small amount of secretion present to act as a culture media.

Acute mastitis may occur in the male and occasionally progresses to abscess formation. Of 3 cases of acute mastitis presented here, in 2 a definite abscess was present. The usual course, however, is that of a subacute infection which tends to progress into a chronic state.

Chronic mastitis is the most frequent cause of enlargement of the male breast. In the female at least three types of "chronic mastitis," based upon anatomical and pathologic findings, are seen (chronic glandular mastitis, chronic interstitial mastitis, and senile involution). In the male breast differentiation cannot well be made; the clinical and pathologic findings resemble more closely the chronic interstitial type of mastitis of females.

In this group of cases there was a visible change, most marked for from 3 to 5 cm. about the nipple. The tumor was tender and freely movable. Except in the acute cases there was no redness. I have never seen any secretion from a male breast, nor could pus be expelled. The axillary glands in chronic mastitis were seldom tender and only slightly palpable.

The microscopic findings of chronic mastitis are slight round-cell infiltration about the ducts, increased vascularity, an edema of the fibrous stroma about the alveoli and ducts, with resulting increase in the fibrous elements. Especially in circumscribed areas, the process may resemble adenofibroma.

One case of this series should perhaps be diagnosed gynecomastia. The smooth rounded breast, approximately 5 inches in diameter, resembled that of a female. However, the evidence for mastitis indicated that chronic infection might have brought about an overproduction of fibrous tissue, so that the so-called gynecomastia was a manifestation of long-continued chronic irritation. In this case, no changes were present in the testicles nor were other sexual characteristics altered, and none should be expected if it is the result of chronic infection.

Treatment of acute mastitis in males does not differ from that encountered in the non-lactating breast of females. Excision of the mammary tissue is the only safe procedure. Carcinoma of the male breast does occur and particularly as the result of long-con-

tinued irritation. The manifestations of the clinical course are so similar and the determination of the actual condition so difficult, that in a large percentage of instances an absolute diagnosis without removal of the breast is impossible. If one is in doubt, and one can hardly be otherwise in the presence of a firm tumor involving a glandular structure, operation is the only safe choice. The chief hope for the reduction of carcinoma in the male breast lies in excision of all breasts showing chronic mastitis. The loss of a non-functioning rudimentary glandular structure is of little importance, and it is far better to sacrifice 10 male mammary glands needlessly, than to allow 1 to progress to malignancy with its resulting serious sequelæ.

Case Abstracts. Case 1.—An engineer, aged 32, stated that he had noticed a swelling of the left breast for about 5 years, which was becoming larger. The tumor was freely movable beneath the nipple and not adherent to the underlying muscle. There was no adenopathy. The temperature was not elevated. The removed tumor appeared to be due to mastitis. Microscopically, the bulk of the mass was composed of dense fibrous tissue in which were scattered well-defined glandular structures, whose epithelium was hyperplastic to the extent of presenting in some areas two or three layers of cells, as is frequently seen in fibroadenoma. Some periductal round-cell infiltration was present. Evidence of malignancy was lacking.

Case 2.—A letter carrier, aged 63, stated that he noticed a swelling of the left breast for 1 month. He stated that the strap of his mail pouch continually rubbed the breast. This he believed was the cause of the swelling. Examination revealed a tumor of the breast 5 cm. in diameter, which was not adherent to the nipple nor to the underlying structures. The tumor was removed. Microscopically, it consisted of dense fibrous tissue through which were scattered small islands of glandular tissue. Some periductal infiltration was present. The ducts were lined by a single layer of epithelium. It was a subacute or chronic mastitis.

Case 3.—A letter carrier, aged 42, stated that for about 1 month he had noticed a swelling of the right breast which was moderately tender. He was left-handed so that he carried his mail bag on his right shoulder and he thought the swelling was due to the rubbing of the strap. Examination showed a tender mass 3 cm. in diameter beneath the nipple. It was not adherent to the underlying structures. The breast was removed. Sections showed hyperplasia of glandular acini usually with two or three layers of epithelium. There was moderate round-cell infiltration in the periductal tissues. The findings were those of a subacute or chronic mastitis.

Case 4.—A man, aged 64, retired, stated that he had noticed a tender swelling of the right breast for about 1 month. Examination revealed a tumor mass approximately 4 cm. in diameter. It was not adherent to the deeper structures. The breast was removed. Sections showed scattered areas of glandular tissue lined by a single layer of columnar epithelium embedded in a stroma of fibrous connective tissue. Moderate periductal round-cell infiltration was present. Impression subacute or chronic mastitis.

Case 5.—A young man, aged 21, stated that he had noticed a swelling of the right breast for the past 2 months. There was some pain and moderate tenderness. Examination revealed a swelling of the breast about 4 cm. in diameter. The breast was removed. Microscopic sections showed a dense fibrous stroma in which were scattered acini with regular formed but

with thickened epithelium. Periductal infiltration of round cells gave evidence of a subacute or chronic mastitis.

CASE 6.—A young man, aged 27, stated that he had noticed a tender lump in the left breast for the past 6 months. There had been little pain but the breast was tender. Examination revealed a small mass beneath the left nipple not adherent to underlying structures. The breast was removed. Microscopically, sections revealed glandular epithelium lined with a single layer of columnar epithelium scattered throughout a dense fibrous stroma. There was moderate periductal round-cell infiltration. Subacute mastitis.

CASE 7.—A man, aged 29, stated that for the past 2 months he had noticed that the right breast was tender and somewhat painful at times. The condition had changed little since the onset. Examination revealed a hard swollen tender mammary gland on the right side. The mass was approximately 7 cm. in diameter. On incising into the gland a small amount of purulent material was expelled. Acute mastitis.

CASE 8.—A man, aged 22, stated that for several years he had noticed a lump in the left breast and that for the past 10 days the swelling had been very tender. Examination showed a breast about 4 inches in diameter resembling in size and shape a female breast. It was apparently tender. The infection subsided with wet dressings, and the patient refused to have the breast removed. Clinically, this case was one of gynecomastia with infection of the breast tissue.

CASE 9.—A man, aged 52, stated that for the past 5 months he had noticed a tumor of the left breast which had increased somewhat in size. There was some tingling pain but no tenderness. Examination showed a mass 7 cm. in diameter which was attached to the overlying skin and to the muscle sheath beneath. The axillary glands were enlarged. Radical removal of the breast and lymph nodes was done. Sections showed adenocarcinoma in both the breast and lymph glands.

CASE 10.—A man, aged 22, stated that 6 months before he had had an empyema drained on the left side. While this was still draining, the right breast became sore and tender. While the tenderness had become less, it continued to annoy him somewhat and slight tenderness persisted. Examination revealed a tender swelling of the right breast 4 cm. in diameter with slight redness of the skin.

CASE 11.—A man, aged 41, complained of a tender swelling of the left breast for the past 3 months. It has grown somewhat during that time. The breast was removed. Sections showed a chronic mastitis.

CASE 12.—A boy, aged 17, stated that the left breast had been large for at least 2 months. He had never noticed any soreness nor other symptoms, but a friend had told him at that time that the one breast looked like a girl's. The breast was removed. Section of the breast showed a fibroadenoma.

CASE 13.—A man, aged 45, stated that 7 weeks previously he had noticed a tender swelling of the left breast. He thought there was some increase in size during the past month. The breast was removed. Sections showed an epidermoid cyst, infected, lying in the mammary tissue.

CASE 14.—A young man, aged 21, stated that 5 months previous he had noticed a tender lump in the left breast which he thought had increased in size. There has been no pain but the breast has remained tender. The breast was excised. Microscopic sections showed a fibroadenoma with some periductal round-cell infiltration.

CASE 15.—A young man, aged 21, stated that 1 month before he had been struck on the left breast. Since then the breast had been tender and somewhat painful. It was removed. Sections showed scattered ducts

lined with simple and stratified columnar epithelium. There was some periductal round-cell infiltration.

CASE 16.—A man, aged 35, complained of a tender swelling of the left breast of 10 days' duration. The tender, swollen breast was excised. Sections showed an acute and subacute inflammation.

CASE 17.—A man, aged 63, under treatment for another condition, complained of a tender swelling of the right breast. Examination showed a firm rounded swelling 4 cm. in diameter beneath the right nipple. There was moderate tenderness. Excision was advised but refused by the patient.

Summary. Seventeen swellings of the male breast are reported, 1 of which was malignant.

The male breast is a well-developed glandular structure, and as such is subject to the same pathologic processes as occur in the non-lactating female breast.

Subacute or chronic mastitis is the pathologic condition most frequently encountered. It may change to fibroadenoma or occasionally to carcinoma.

Treatment of chronic mastitis in the male should include excision of the mammary tissue, as the loss of a rudimentary gland is of little importance and carcinoma may thus be prevented.

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THE DIAGNOSTIC VALUE OF SUPRAVITAL STAINING IN INFECTIOUS MONONUCLEOSIS.

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GLANDULAR fever was long confused with a relatively large group of diseases producing generalized lymph node and splenic enlargement. It was not until 1920, that the clinical syndrome, the characteristic blood picture, and the benign course were correlated by Sprunt and Evans who coined the term infectious mononucleosis.[16] The hematologic characteristics were thoroughly investigated by Downey, [6,7a,b] Baldridge, Rohner, and Hansmann,[1] Nyfeldt,[13] and Lehndorff and Schwarz.[10]

As medical consciousness of the disease waxed, the difficulty of definitely distinguishing it from several other disease entities be-

came evident. Note was variously made concerning resemblances to leukemia, tuberculosis, Hodgkin's disease, agranulocytic angina, Vincent's angina, and postinfectious lymphocytosis. In 1932, however, Paul and Bunnell[14] accidentally recognized the presence of heterophile agglutinins and hemolysins for sheep cells in patients suffering from the disease and subsequent clinical application has revealed considerable specificity of this reaction.[5,17,18] Although the agglutinins occur under a variety of circumstances[14,17] and on occasion may not be present in this disease,[4b,c] they have proved a definite aid in distinguishing infectious mononucleosis from the diseases for which it may be mistaken. In fact, the clinical manifestations of the disease are so variable that a recognition of its presence depends entirely upon both serologic and morphologic study of the blood.

Unfortunately, as the result of increasing emphasis upon the serologic aspect of diagnosis associated with the apparent difficulty of the unpracticed, and all too frequently, the practiced eye in definitely identifying the predominant cell in the peripheral blood,[2,4a,9,15,20] the marked variation in the clinical syndrome, and confusing references to non-mononuclear types and phases of mononucleosis, the heterophile antibody reaction is rapidly being accepted as the prime and occasionally sole factor in diagnosis.[17] This has created a recognizable trend toward removing the establishment of the diagnosis from the province of the physician and placing it into the hands of the laboratory technician. Excessive reliance, however, upon any single laboratory procedure, regardless of how well understood and tested it may be, has always proved dangerous in any diagnostic field. An additional criterion, if simply applicable, and confirmed in reliability, must therefore, have practical value. With this in mind, note will be made of readily elicitable morphologic features which serve to establish with ease and rapidity the identity of infectious mononucleosis.

It has been claimed that certain criteria manifest themselves in the appearance of the specific cell of the disease, but in view of the varied nomenclature employed (atypical lymphocyte, immature lymphocytes, lymphoblast, monocyte, mononuclear cell, etc.), it is evident that widespread confusion exists concerning its identity. Despite the increasing interest in the disease, little attention has been directed toward the appearance of the living cells, a state in which they may be conclusively diagnostic. McLean,[12] Nyfeldt,[13] and Wilson and Cunningham[20] have described the appearance of the cells of infectious mononucleosis when stained supravitally by neutral red and Janus green. The method which has a very definite value in supplementing the ordinary clinical measures, will readily confirm the diagnosis of infectious mononucleosis.

Material and Methods. One or more blood specimens obtained from each of 21 individuals suffering from subsequently proved infectious mono-

nucleosis were studied by fixed smear and moist supravitally stained preparations. Ordinary slide smears of peripheral blood were dried in air and stained with a combination of Wright and Giemsa stains. Blood obtained from the same puncture wound was in each case placed upon 3 clean glass slides—one bearing a dried film of neutral red and Janus green, another a film of neutral red alone, the third slide containing no dye at all. Each drop of blood was covered by a thin coverslip applied without pressure. The method has been described in detail elsewhere.[8] Such preparations even without sealing or warmth remained adequate for study for as long as 2 to 4 hours. The warm box offered little advantage except for studies of cell motility and was therefore utilized only for such observations. At room temperature adequate staining of cytoplasmic structures occurred within 15 to 20 minutes and a temperature of 37° C. motility was evident in about 10 minutes.

Each of the cases had determinations of the heterophile antibody titer and all except one showed titers within the range established by Davidsohn,[5] Paul and Bunnell,[14] and van Ravenswaay[18] as being that commonly found in the disease. The one exception presented clinical and hematologic criteria unmistakably characteristic of glandular fever, although at no time were there evidences of sheep cell agglutinins above a dilution of 1 to 30. Such exceptions have been noted previously.[4b,c] The absence of heterophile agglutinins was consistently observed in many other cases with less characteristic lymphocytoses.

Observations. A. *Refractile Granules.* In the course of earlier observations there had been noted within circulating lymphocytes a peculiar refractile granule visible in unstained preparations and assuming a mahogany tint with neutral red.[8a] Subsequent studies established the constancy of the occurrence of these granules in approximately $\frac{1}{3}$ of lymphocytes in wet preparations.[8b] Confirmatory observations have since been published by Whitby and Hynes.[19] In conjunction with the present series of cases of infectious mononucleosis, moist blood preparations have been obtained from 137 additional individuals and have been examined with particular reference to the presence of refractile bodies. In accordance with the preëxisting data they were present relatively constantly in more than 25% of the lymphocytes. This group included 52 normal persons and 85 patients with a variety of diseases. On rare occasions the granule-bearing cells have been fewer than 25% of the total number of lymphocytes, but in only 9 did they constitute less than 20%. No question of diagnosis arose in any of these exceptional cases since all had lymphocytes well within the normal range numerically and morphologically. In the great majority of the remainder the refractile bodies were present to the extent of 30 to 50%, the average for the entire 137 cases being 31.1%.

In a previous publication note had been made of a single exception to this rule wherein the percentage of granule-bearing lymphocytes was less than the established minimum.[8b] This blood had been obtained from a case of infectious mononucleosis and with interest thus directed the 20 additional cases in the present series were examined with the intent of determining the frequency of the pecu-

liarity in this disease. In none were the lymphocytes containing granules in excess of 15% during the acute disease, nor was there any striking variation of this phenomenon in either the apparently normal or obviously abnormal cells, the former exhibiting as much of a diminution of granules as the latter.

In seeking for these cases of glandular fever opportunity to examine bloods from cases resembling it in one way or another was afforded in 33 instances. The cases included in this subgroup presented lymphocytoses between 30 and 88%. Several of these specimens were obtained from infants and young children. In

TABLE 1.—LYMPHOCYTES AND THEIR GRANULES IN VARIOUS DISEASES.

Group.	Subgroup.	No. cases.	Average % lymphs.	% granule lymphs.	Max.	Min.	< 20% granules	< 15% granules
I Lymphomatoid diseases	Lymphosarcoma	3	18.7	39.0	45%	34%	0	0
	Hodgkin's	3	17.2	40.7	45	27	0	0
II Miscellaneous blood dyscrasias	Aplastic anemia	2	31.0	37.0	42	32	0	0
	Pernicious anemia	1	42.5	34.0	..	..	0	0
	Hypochromic anemia	2	21.5	38.5	41	36	0	0
	Purpura hemorrhagica	5	16.4	34.6	46	15	1	0
	Polycythemia vera	1	26.0	57.0	..	..	0	0
III Leukemia	Myelogenous	8	7.6	44.4	61	33	0	0
	Lymphatic	7	69.0	35.0	47	18	1	0
	Plasma cell	1	88.0	15.0	..	..	1	0
IV Normal	.....	52	....	34.0	57	14	4	1
V Tuberculosis	Miliary	1	10.5	47.0	..	..	0	0
	Peritonitis	1	28.0	35.0	..	..	0	0
	Pulmonary	14	14.7	34.0	52	22	0	0
VI Infectious diseases	Acute	17	23.7	38.0	69	16	1	0
	Subsiding	7	37.0	33.5	47	20	0	0
VII Miscellaneous	.....	11	23.0	37.0	54	19	1	0
VIII Infectious mononucleosis	.....	21	63.2	11.2	15	5	21	21

many, reasonable clinical doubt as to differentiation from infectious mononucleosis had existed. In only one of the group, however, did the granule-bearing lymphocytes approach the critical minimal level and this was a case of aleukemic plasma-cell leukemia. The appearance of the component elements of this blood smear, however, was such that confusion with infectious mononucleosis was impossible. Graphic representation of this group is demonstrated by Group IX in Figure 1.

Analyses of the percentages of granule-bearing lymphocytes present in the various groups accumulated are shown in Table 1 and Figure 1. The wide range of the percentages in the normal group and those diseases exclusive of infectious mononucleosis is in sharp

distinction to the group of infectious mononucleosis. Reference to the minimal levels in the control Groups I to VII demonstrates the sparsity of bloods containing fewer than 20% lymphocytes with refractile granules. In contradistinction to these groups, Group VIII, consisting of the 21 cases of glandular fever, shows a maximal

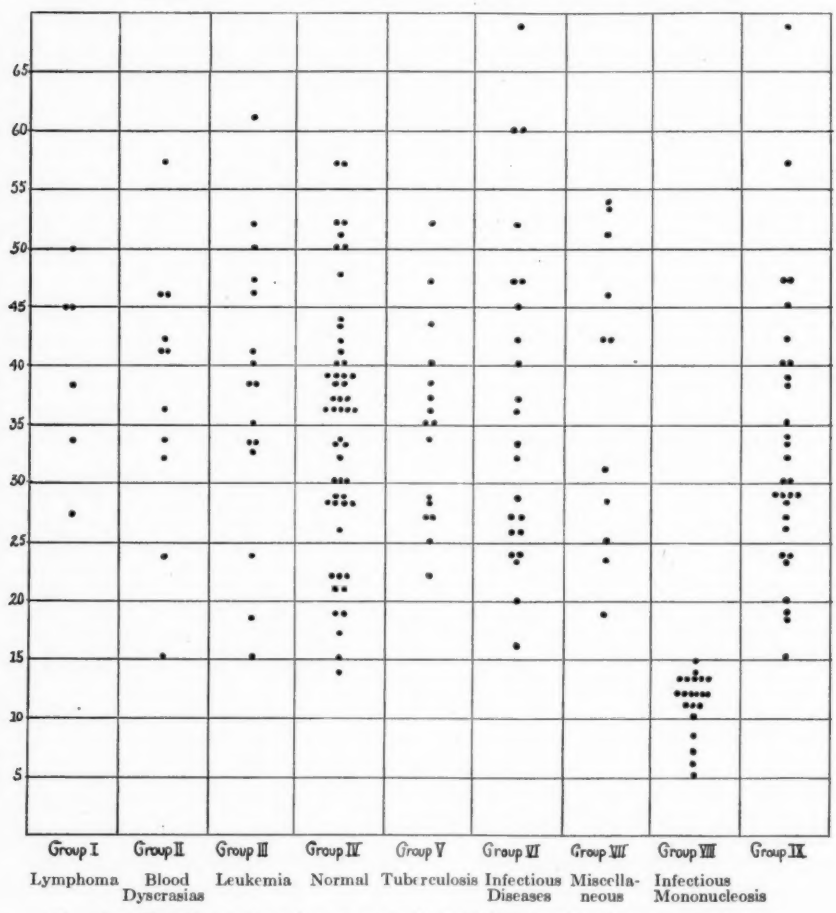

Fig. 1.—The diagnostic value of supravital staining in infectious mononucleosis.

level of 15% with an average content of 11.6%. Equally striking was the persistence of this dearth of granule lymphocytes for several weeks to months after the disease had subsided clinically. Marked variation in the length of time required for subsidence of minor clinical evidences of the disease has been noted in the literature.[1,11,14,16]

Ordinary moist unstained preparations were adequate for identification of the refractile granule-bearing lymphocytes and approximately 30 minutes were necessary to perform a differential count of 200 cells. Facility in recognizing the various cells was naturally enhanced, however, in those preparations stained with neutral red and Janus green and certain other characteristics were demonstrated which warrant detailed description.

B. *Supravital Studies.* The cells in infectious mononucleosis varied considerably in size and shape and most of them showed motility at one time or another when kept at 37° C. and not infrequently at room temperature as well. The motility was always lymphocytic in character inasmuch as the nucleus remained at the fore end of the moving cell and the cytoplasm streamed behind in a tail-like fashion. At no time was the surface film movement distinctive of monocytes observed in these cells.[8a] The presence of Janus green in the stain film inhibited motility markedly.

Nuclei were relatively large, eccentric, and filled from one-half to three-fourths of each cell. The configuration was generally reniform although in the motile cells and the small immobile lymphocytes bizarre contours predominated. Chromatin, which was only visible with lessened illumination, exhibited a coarse smudgy appearance and a fluted or grooved arrangement of the chromatin strands was frequently perceived. No nucleoli or mitoses were encountered but occasionally a nucleus in the process of amitotic division or two discrete nuclei in a single cell were seen. Occasional lymphocytes contained nuclei indistinguishable from those in plasma cells, with coarse clumped chromatin smudges frequently aggregated at the nuclear margin and a comparatively thick, slightly refractile nuclear membrane. These cells were similar in all other respects to the lymphocytes encountered in this disease.

The cytoplasm generally presented the characteristic hazy, faintly opaque appearance of normal lymphocytes distinctive from the finely granular, ground glass cytoplasm of the monocyte. The mitochondria in the small lymphocytes and many of the intermediate lymphocytes were moderately coarse, short, rod-shaped, and globular particles staining bright greenish blue with Janus green. These were exactly similar to those observed in normal lymphocytes but in the remainder of the intermediate and all of the large lymphocytes the mitochondria were predominantly rod-shaped, slightly less numerous, and considerably larger than in the normal cell. Furthermore, although a few of the smaller mitochondria remained in the vicinity of the nuclear border and frequently appeared to be superimposed upon the nucleus, the majority were dispersed throughout the cytoplasm in the portion contiguous with but peripheral to the bay of the nucleus. In the immobile cells they had the appearance of particles of bright bluish-green opaque substance suspended in a faintly yellowish, translucent gelatin. Such a cell

(Fig. 2) was demonstrated by Wilson and Cunningham[20] in a case of hemolytic streptococcus sore throat which from the scant data appended might equally well have been infectious mononucleosis.

Neutral red bodies were generally increased in number but retained the bright red refractile appearance normally noted in lymphocytes. These were generally distributed but exhibited a very pronounced tendency to clump on one side of the indented nucleus within its bay. They did not possess the regular arrangement of the true rosette appearing in the rabbit monocyte and less frequently in the human monocyte. This aggregation was therefore considered to be a pseudorosette. Such cells have been noted very occasionally in normal blood but never so frequently as they appear in infectious mononucleosis. Surrounding the neutral red aggregations there was usually an irregular halo of sparsely clustered mitochondria which rarely intruded upon the space occupied by the pseudorosette. In the motile cells the neutral red bodies retained their proximate relationship to one another behind the nucleus although the bay was usually obscured. Frequently the cytoplasm contained one to ten unstained vacuoles.

Distinction from the monocyte was therefore relatively simple, nor was there sufficient similarity to the immature lymphocytes to preclude differentiation. Lymphoblasts were similar in size but their nuclei were less frequently indented and usually filled more of the cell. The chromatin was less coarse, more regularly arranged, and nucleoli were usually evident. Neutral red bodies were not present and mitochondria were finer and clustered about the nuclear border. Occasionally such a cell was observed in infectious mononucleosis. Lymphocytes present in lymphocytic states such as pertussis and postinfectious lymphocytosis constantly adhered to the normal pattern. Details relative to the characteristic morphology of the cells cited above are enumerated in an earlier publication.[8a]

C. *Dried Smears.* Cursory studies of fixed blood smears in this series revealed a predominance of those cells classed as Type I by Downey.[6,7a,b] These were not, however, deemed sufficiently characteristic to warrant differentiation from such cells as were seen in the postinfectious lymphocytoses and other lymphocytic states wherein large and intermediate lymphocytes made their appearance in large numbers. Furthermore, similar cells were abundant in the blood of normal infants and young children. Major distinction became sharply evident in the majority of cases only when the cells were viewed in the living state, stained supravitally. Confusion of the Type I lymphocytes in the fixed smears with the lymphoblasts present in lymphatic leukemia was, however, minimized. The differential features outlined by Downey generally sufficed to establish distinction.

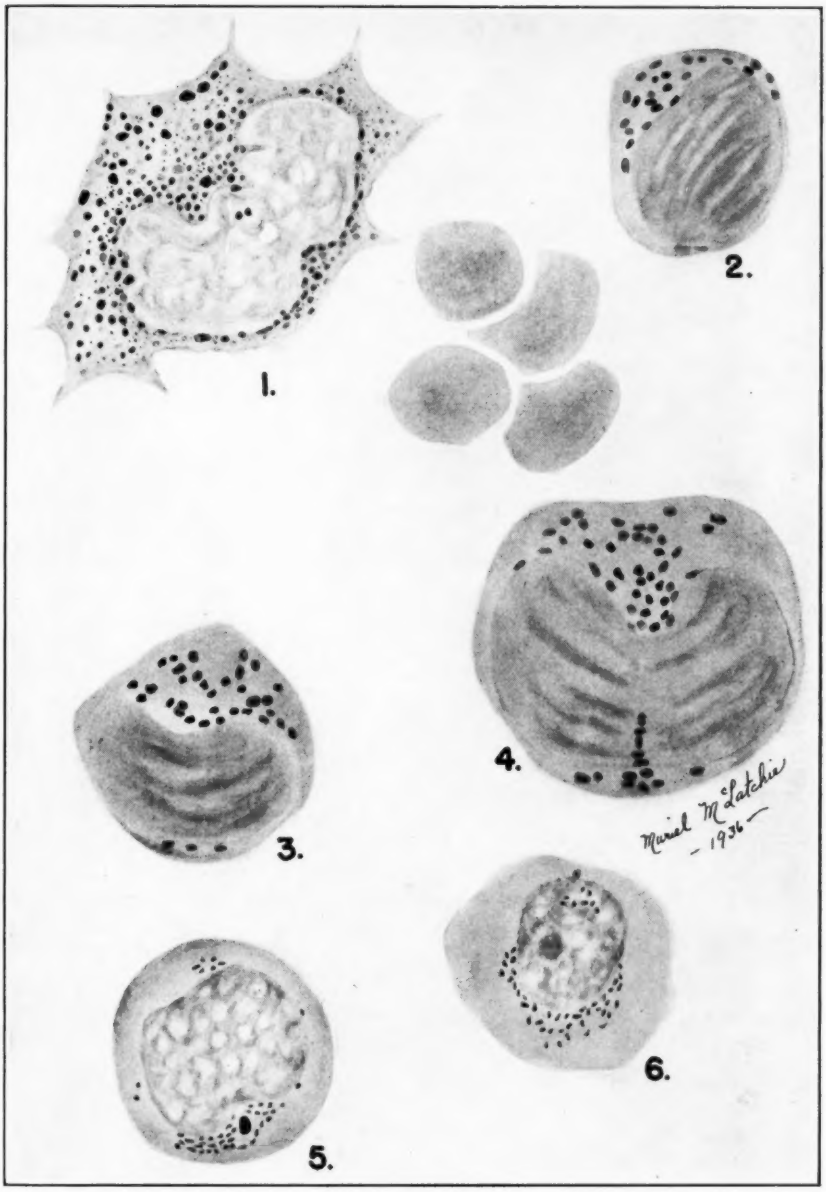

FIG. 2.—1, Normal monocyte. Note diffusely scattered mitochondria and neutral red bodies varying widely in size. 2, Small lymphocyte from a case of infectious mononucleosis. The mitochondria are coarse and the chromatin grooved in appearance. 3, Intermediate lymphocyte in infectious mononucleosis. 4, Large lymphocyte in infectious mononucleosis. Neutral red bodies tend to congregate within the nuclear concavity to form a pseudorosette. 5, Normal lymphocyte. Chromatin is smudgy and finer mitochondria exhibit characteristic clumping. A single refractile body is present but there are no neutral red granules. 6, Lymphoblast. Mitochondria are grouped loosely about the nuclear border. Chromatin is relatively fine and a single nucleolus is present.

NOTE. A small clump of red blood cells is shown for size contrast. The red of the neutral red bodies and the blue of the mitochondria in the original colored illustration are naturally less distinct in monotone.

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Discussion. Despite the contrary claims of Downey and his associates,[6,7a,b] it is evident that very definite difficulty may exist in differentiating the blood picture of infectious mononucleosis from that of other diseases producing a lymphocytic response.[2,3,4,9,15,20] Certainly, in view of the reasonable doubt expressed by individuals who have repeated contact with the disease, it is not too much to expect that those who encounter it less frequently will have considerably greater difficulty. Under such circumstances it is not surprising that so much stress is being applied to the presence of heterophile antibodies as a diagnostic measure. The test is unquestionably a valuable one, but it is occasionally geographically impractical and may be time consuming and relatively expensive. Furthermore, it is felt that application of the observations noted above will obviate to a certain degree the necessity of performing the test.

The characteristic lymphocyte of infectious mononucleosis is sufficiently distinctive in the living state to allow sharp differentiation from the cells present in lymphatic leukemia, infectious lymphocytosis (pertussis, etc.), and such monocytic reactions as occur in active tuberculosis. This is much less the case in the dried blood film. Its motility, protoplasmic content, and nuclear structure qualitatively proclaim the cell a lymphocyte, and the structural arrangement of these elements definitely establish it as a relatively mature but atypical cell. With regard to the postinfectious lymphcytoses and other clinical states with which the disease might conceivably be confused, the unique, constant, absolute decrease of lymphocytes bearing the specific refractile granules is a striking differential point. The term "absolute" is used advisedly for although both atypical and perfectly normal lymphocytes are present, the diminution of the refractile bodies is evident in both. It follows, therefore, that although otherwise normal such cells are lacking in structures present in all other conditions investigated. Table 1 and Figure 1 demonstrate the fact that specimens obtained from individuals with glandular fever never show extension of granule-bearing lymphocytes above the determined minimal normal level of 15%. This condition is sufficiently limited to infectious mononucleosis to warrant its utilization as a contributory diagnostic measure.

In view of the marked variance of prognostic significance attached to infectious mononucleosis and the many diseases which may at one time or another resemble each other both clinically and hematologically, the advisability of utilizing as many clinical diagnostic measures as may be available is evident. Although the determination of the presence of heterophile antibodies generally offers adequate confirmation, it is neither an absolute nor always a convenient diagnostic procedure. Other means of confirming clinical suspicion of glandular fever under conditions of minimal convenience are therefore not amiss. Conclusive diagnosis may be accomplished

by recognition of the characteristic supravitally stained blood cells and by determining the specific decrease of refractile granule-bearing lymphocytes regularly occurring in this disease.

Summary. 1. There is fairly generally admitted difficulty in definitely identifying the specific cell of infectious mononucleosis.

2. Despite the evident value of the determination of the presence of heterophile agglutinins, recognition of characteristic morphologic features of the typical cell of the disease would obviate its use to a great extent. Such features are evident in supravitally stained preparations.

3. By this means the cell is definitely shown to be an atypical but relatively mature lymphocyte readily distinguished from other mononuclear cells by several characteristics.

4. Refractile granules present in one-third of lymphocytes in other diseases and in the normal state are never present in higher than 15% of the lymphocytes in infectious mononucleosis.

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THE EFFECT OF THE INTRAVENOUS INJECTION OF HYPERTONIC DEXTROSE SOLUTION UPON THE CEREBROSPINAL FLUID PRESSURE IN CASES OF BRAIN TUMOR.

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The intravenous injection of hypertonic dextrose solution as a means of dehydration in cases of increased intracranial pressure is quite general. The object of the study to be reported here was to determine the actual effect of such injections upon the cerebro-

spinal fluid pressures and hence upon the intracranial pressures in cases of brain tumor.

The original view of Faivre[2] that the cerebrospinal fluid is unlike any of the other body fluids with the exception of the aqueous humor of the eye, is accepted by many physiologists. The manner in which the fluid is formed is a matter of dispute. Earlier workers, among them Magendie,[14] believed that it was formed by the leptomeninges. Faivre suggested that the cells of the choroid plexuses of the ventricles were concerned with its formation. Weed[19] and others suggested that perivascular tissue within the nervous system may contribute to the formation of the fluid. There is evidence also that ventricular ependymal cells in regions other than those of the choroid plexuses may secrete cerebrospinal fluid. This question has not been settled.

Likewise there has been no general agreement as to the route by which this fluid reaches the general circulation from the subarachnoid spaces. Key and Retzius,[11] and Weed,[19] found that the major drainage occurs along the Pacchionian bodies, and that a slower drainage into the lymphatic system takes place along certain emergent nerves. The greater part of the cerebrospinal fluid escapes directly into the venous sinuses of the dura. Forbes, Fremont-Smith, and Wolff[5] have shown that the direction of flow of the cerebrospinal fluid through the choroid plexuses may be reversed by increasing the osmotic pressure of the blood. They believe that the choroid plexuses may be regarded as semipermeable membranes and that the cerebrospinal fluid is a true dialysate. The plexuses would thus form a part of the mechanism for regulating intraventricular and intracranial pressure. Gamble[6] has shown, and is so quoted by Fay,[3] that the fluid interchange between the vascular and interstitial compartments is facilitated by the fact that both are dependent upon a fixed base sodium for retention; whereas intracellular fluid is maintained by the fixed base potassium, and exchanges are not reciprocal. Therefore when fluid intake is restricted and elimination is forced, it is necessary that the interstitial reservoirs be drawn upon in order that the fluid volume may maintain its integrity. This is the principle upon which reduction of intracranial pressure by means of dehydration is based.

Reduction of brain volume and cerebrospinal fluid pressure by means of the intravenous injection of hypertonic solutions of various salts and of glucose was accomplished by Weed and McKibben[20] in 1919. They found that the bulk of the brain could be controlled by a change in the concentration of certain elements in the blood stream which resulted in absorption of water from the tissues. In their work with cats they showed that the intravenous injection of hypertonic solutions caused an initial rise in the cerebrospinal fluid pressure which was followed immediately by a marked fall in pressure. Cushing and Foley[1] achieved like results. Foley and Putnam[4] obtained similar effects by intraintestinal administration of hyper-

tonic solutions. In 1932, Milles and Hurwitz[18] reported from animal experimentation that the reduction of cerebrospinal fluid pressures from single doses of dextrose was transient, and that a secondary rise occurred which reached a point much higher than the original level.

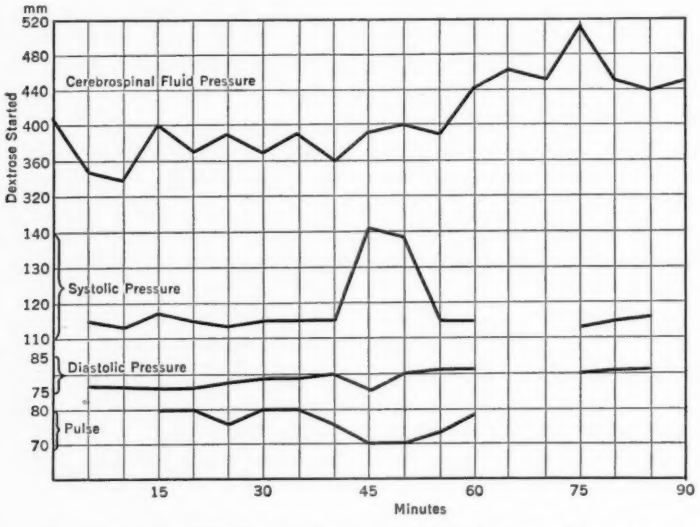

CHART I.—No. 308536. Brain tumor, right posterior frontal region.

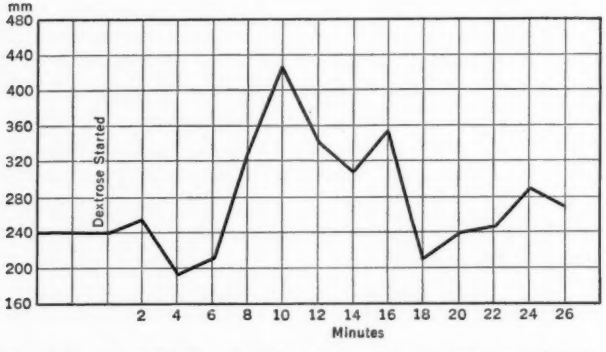

CHART II.—No. 306897. Spindle-cell sarcoma, right temporal region.

Kubie[13] believed that there was a correlation between intracranial blood volume and intracranial pressure but not between the pressures themselves. Wolff and Forbes[21] have shown that the administration of hypertonic solutions intravenously is followed by diminution of the caliber of the arterioles and venules of the pia, and that conversely, hypotonic solutions cause dilatation of the

TABLE 1.—CEREBROSPINAL FLUID PRESSURES FOLLOWING THE INTRAVENOUS INJECTION OF 50% DEXTROSE SOLUTION.

TABLE 1.—CEREBROSPINAL FLUID PRESSURES FOLLOWING THE INTRAVENOUS INJECTION OF 50% DEXTROSE SOLUTION.

Case	Case No.	Age.	Sex.	Clinical diagnosis.	Amount dextrose injected (cc.).	Cerebrospinal fluid pressures in mm. water.				Pathological diagnosis.	Remarks.
						Initial.	Minimum.	Maximum.	At end of experiment.		
1	308536	28	M.	Right posterior frontal tumor	100	410	350 (30 min.)	530 (86 min.)	450	No report	Choked disk, O.D. 4½D.O.S. 6D. Blood pressure, systolic, 112–116, diastolic 88–80, pulse, 76–80.
2	293485	43	M.	Right frontal tumor	50	210	210 (at start of exper.)	260 (30 min.)	245	Meningeal epithelioma	Bilateral optic atrophy; no appreciable change in pulse and blood pressure.
3	309026	18	F.	Left parietal tumor	100	185	125 (45 min.)	340 (90 min.)	340	Calcified glioma	Normal ocular fundi with contraction visual fields; no appreciable change in pulse or blood pressure.
4	309155	24	M.	Left parietal tumor	60	225	210 (5 min.)	260 (20 min.)	250	Spindle cell carcinoma	No appreciable change in blood pressure; pulse dropped from 90 to 64 in first 5 minutes; gradually rose to 72.
5	304866	34	M.	Temporal lobe tumor, left	100	175	160 (38 min.)	195 (5 min.)	178	Angioma	Ocular fundi neg. Blood pressure unchanged; only slight variation in pulse.
6	306897	46	M.	Right temporal lobe tumor	50	240	195 (5 min.)	430 (14 min.)	270	Spindle cell carcinoma	Choked disk, O.D. 2D. Pulse dropped from 56 to 44. Patient did not rouse from coma.
7	292284	37	M.	Old skull fracture	100	115	115 (start of exper.)	220 (75 min.)	200	No report	Decompression 2½ x 1½ in. Ocular fundi neg. Only slight variation in blood pressure; pulse 98–96.
8	307590	42	M.	Gumma of brain. Positive Kahn	50	270	115 (68 min.)	270 (start of exper.)	130	No biopsy	Choked disk, O.U. 4D. Only slight variation in blood pressure.
9	309175	30	F.	Gumma of brain. Treated case. Serology neg.	100	380	250 (25 min.)	520 (90 min.)	520	No biopsy	Choked disk, O.D. 4½D; left optic disk hyperemic. Pulse variation 68–84; blood pressure 110/84; patient did not rouse from coma.

vessels. Kubie and Hetler[12] demonstrated, by means of color photography, that following the intravenous injection of hypertonic solutions there is a narrowing of the vessels of the pia coincident with dilatation of the vessels of the cortex itself. It is probable that the total volume of the intracranial blood is increased as the volume of the intracranial fluid is diminished by the action of the hypertonic solution.

Varying results have been reported from the clinical use of hypertonic glucose solutions administered intravenously. Grant[7] stated that the intravenous injection of 50% glucose produced a lowering of the cerebrospinal fluid pressure which was stationary providing the patient coöperated well. Masserman[15] studied the effect of the administration of isotonic solutions in effective concentrations in 85 normal patients. He found that there was an initial increase in the cerebrospinal fluid pressure which was followed first by a fall in pressure and then by a secondary rise to levels which were from 8 to 148 mm. of water above the normal pressure. Jackson *et al.*,[9] showed that in cases of injury to the brain, intracranial pressure not only may be appreciably lowered by the intravenous injection of hypertonic dextrose solutions, but may also be increased. He found an immediate increase in pressure in half of his cases and a slight temporary reduction of the pressure in the other half of his cases. In all cases there was a secondary rise in pressure after from 15 to 30 minutes. This secondary increase in pressure he considered to be due to pressure on the return venous flow in the sinuses of the brain.

Material. The material used for this study was composed of 6 cases of brain tumor in which the diagnosis was confirmed by subsequent surgery and pathologic report of the specimen, 2 cases of gumma of the brain, and 1 old skull fracture. In all cases there were two or more indications of increased intracranial pressure. Only the readings of the patients who were able to coöperate and remain quiet for the duration of the examination were used for the study. The technique employed was as follows: The patient was placed on his side and made as comfortable as possible without a sedative. After the spinal puncture needle had been inserted between the second and third lumbar vertebræ, with as little loss of cerebrospinal fluid as possible, a water manometer was connected with the needle and held in place for the duration of the test. As soon as a constant cerebrospinal fluid pressure was obtained, from 50 to 100 cc. of a 50% dextrose solution was injected slowly into the vein. Manometer readings were taken every 5 seconds for 5 minutes and every 15 seconds thereafter for periods up to 2 hours in length. Blood pressure readings were taken throughout the examination. No other method of dehydration was used either before or during the examination.

Results. The results of this study are shown in the accompanying table. The data show that in only one case was the cerebrospinal fluid pressure reduced by the intravenous injection of 50% dextrose solution, without reaching, at some time during the experiment, a higher level than that of the original pressure. In one other case

there was an initial fall followed by a rise and in 7 cases there were initial rises in pressure. Subsequent falls in pressure were observed in some of these but secondary rises brought the pressure at the end of the experiment to a higher level than was observed before the injection of the dextrose solution. In only one case was the pressure lower at the end than at the beginning of the examination.

My explanation of these variations in cerebrospinal fluid pressure is that this pressure is elevated by the oxidation of the injected dextrose solution which draws the fluid from the body tissues and releases it by osmosis to the circulation. As more fluid is drawn into the circulation, the cerebrospinal fluid pressure increases, and *vice versa*.

These studies show that in cases of brain tumor the results of the intravenous injection of hypertonic dextrose solution upon the pressure of the cerebrospinal fluid are variable. The method may be tried in cases in which a rapid drop in pressure is desired but such a result cannot be assured. This procedure should be supplemented by other clinical methods of dehydration such as limitation of fluids by mouth and the purging use of magnesium sulphate either by mouth or by enema.

Conclusions. 1. The intravenous injection of hypertonic dextrose solution in cases of brain tumor sometimes reduces the cerebrospinal fluid pressure temporarily within the first 2 hours after injection; in most cases it causes an increase in pressure at some time during this period.

2. The intravenous injection of saturated dextrose solution cannot be depended upon, in itself, to reduce the cerebrospinal fluid pressure in cases of brain tumor.

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VASODEPRESSOR ACTIVITY OF BLOOD OF NORMAL AND BURNED DOGS. CRITICISM OF METHOD.

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Proof of the existence of appreciable quantities of blood histamine in normal animals has rested upon: 1, a few chemical analyses, and, 2, the production by blood extracts of characteristic effects on isolated tissues and of vasodepression in the cat.

In addition to the foregoing methods, in burned animals, blood and tissue extracts have been injected into normal animals and the resulting symptoms observed. For the actual extraction of histamine from tissues, various methods have been used.

Reports have varied widely concerning the quantity of histamine in blood. Koessler and Hanke[5] and Phemister and Handy[6] found no histamine definitely present in blood; while Harris,[4] Best and McHenry,[2a] and Barsoum and Gaddum[1] found it present in appreciable quantities.

Pharmacologic assay of tissue histamine is especially difficult because substances such as peptone, acid hydrolysis products of protein, choline, acetylcholine, adenylic acid and related compounds —either initially present or else formed during the preparation of the assay solution—also lower the blood pressure of the assay animal.

In view of the difficulty of extracting tissue histamine and because of the vasodepressor action of the various substances present in the extracts, it was deemed advisable to examine critically the extraction method most commonly used.

Experimental. The assay solution of normal dog's blood, as well as a sample of the cat's own blood and an egg albumen solution, was prepared by the method of Best and McHenry.[2a] Ether was not used to anesthetize the assay cat, because of the difficulty in maintaining even anesthesia throughout the experiment. Instead, sodium pentobarbital, 28.6 mg. per kilo of body weight, was injected intravenously.

In the assay, precautions pointed out by Burn[3a,b] were observed. The assay solution (not more than 2 cc. per kilo of body weight) was injected into the femoral vein. Blood pressure, period of injection, and time in seconds were recorded. Injections were not repeated within 5 minutes. In each case the blood pressure was allowed to approximate its initial level. Exact quantities of histamine acid phosphate were injected to give a fall in blood pressure comparable to that produced by the assay solution.

The vagi were paralyzed with atropine sulphate and then stimulated by an induced current to prove the effectiveness of the atropinization.

The assay solution was again injected. If vasodepression resulted, then pure histamine was injected intravenously in a quantity sufficient to lower the blood pressure to the same extent.

Burning. The dog was anesthetized and 20 cc. of blood drawn. Without allowing it to regain consciousness, the animal was then burned over approximately one-third of its body surface. After the lapse of a definite interval of time, 20 cc. of blood were drawn. Each sample of blood was prepared[2a] and assayed in the same manner as the normal dog's blood.

Results. In general, the assay solutions gave a type of blood pressure curve entirely different from that produced by histamine. The onset of the blood pressure fall was immediate with histamine, but with the assay solutions it was delayed. Atropine did not affect the histamine fall but markedly reduced the fall produced by the assay solutions.

TABLE 1.

B. P. before injection (mm.).	Latent period until principal fall (sec.).	Injection rise to (mm.).	Primary fall to (mm.).	Secondary rise to (mm.).	Secondary fall to (mm.).	Cat No.	Solution No.
108	5.0	108	66	...	...	19	H6
100	5.0	100	60	...	...	19	H6A
128	6.0	140	96	...	...	15	H4A
170	13.0	180	154	166	104	18	U1
118	26.0	118	118*	118	90	18	U1A
190	26.0	194	182	184	100	23	GG1
112	20.0	130	112*	112	92	23	GG1A
154	22.0	158	148	148	86	23	HH1
120	24.0	130	120*	120	88	23	HH1A
164	13.0	180	124	164	58	19	V1
106	25.0	122	80	126	76	19	V1A

* Primary fall eliminated by atropine.
Solutions:
H6—Histamine, 0.01 mg. per kilo (before atropine); H6A—same after atropine; H4A—0.001 mg. (after atropine).
U1—Extract of egg albumen (0.032 gm.) before atropine; U1A—same after atropine.
GG1—Normal dog's blood extract (0.25 cc.) before atropine; GG1A—same after atropine.
HH1—Burned dog's blood extract (0.32 cc.) before atropine; HH1A—same after atropine.
V1—Cat's own blood extract (0.34 cc.) before atropine; V1A—same after atropine.

Assay solutions of blood from burned dogs showed little quantitative, and no qualitative, differences in blood pressure effect from those of the same dog before burning.

The albumin extract solution produced the same type of fall as the assay solution prepared from blood. The cat's own blood, prepared in the same manner as dog's blood, produced a marked vasodepression, very similar to that of the dog's blood assay solution.

Data shown in Table 1 are representative of the results obtained in all the assays. Histamine, 0.01 mg. per kilo, caused a fall in blood pressure beginning in 5 seconds and reaching 42 mm. Before atropinization, the assay solution of normal dog's blood caused a fall in blood pressure of 90 mm., beginning 26 seconds after injection. After atropinization, the same solution caused a fall of only 20 mm. beginning in 20 seconds.

The assay solution of blood from burned dogs, before atropinization, produced a fall of 68 mm., beginning 22 seconds after injection. After atropinization, the same sample produced a fall of 32 mm., beginning in 24 seconds. The albumen extract before atropinization produced a primary fall of 16 mm. with a latent period of 6 seconds and maximum fall of 66 mm. after 13 seconds, whereas the same extract, after atropinization, caused a fall of 28 mm., with a latent

period of 26 seconds. The assay solution of the cat's own blood, before atropinization, produced a primary fall of 40 mm. and a maximum fall of 106 mm. with a latent period of 13 seconds. After atropinization, the maximum fall was 30 mm.

Discussion. Best and McHenry[2b] have stated that "the inference that histamine is present is legitimate if the results of a complete physiologic analysis of a solution are identical to those obtained with pure histamine." It is evident that histamine is not responsible for the vasodepression produced by these assay solutions. The long latent period suggests that the vasodepressor substance was formed or liberated in the test animal from the solution injected, and was not present as such in the solution. This long latent period alone is sufficient to eliminate histamine as the cause of the fall in blood pressure.

Additional evidence that histamine is not the responsible factor is furnished by the changed effect following atropine. Furthermore, the curve produced by the assay solution is different in appearance from that produced by histamine in doses sufficient to give a comparable fall in blood pressure. Again, if histamine were the responsible factor, the cat's own blood should not contain sufficient histamine to produce vasodepression when prepared as a diluted assay solution.

Assay solutions of the blood of burned dogs, in most instances, produced no greater vasodepression than assay solutions of normal dog's blood. In those instances in which the fall was greater, the increased fall may be explained by the concentration of blood with concentration of blood protein due to fluid loss in the burned animal.

Protein is the common factor in the substances prepared as assay solutions. Since acid hydrolysis can occur during the preparation, the substance, or substances, responsible for the fall is possibly a product of the protein hydrolysis. Vaughan[7] showed that such protein split products may bring about vasodepression.

Summary. 1. The fall in blood pressure, caused by assay solutions prepared from blood of normal and burned dogs by the Best and McHenry method, is not due to histamine.

2. The increased vasodepression produced by assay solutions of blood of dogs following burns is accounted for by the increased blood protein concentration due to fluid loss.

3. The vasodepressor action of the solutions is possibly caused by a protein split product formed from blood protein during the preparation of the assay solution.

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BOOK REVIEWS AND NOTICES.

HISTORY OF CHINESE MEDICINE. Being a Chronicle of Medical Happenings in China from Ancient Times to the Present Period. By K. CHIMIN WONG, Licentiate of Medicine and Surgery, Hongkong, etc., and WU LIEN-TEH, M.A., M.D. (CANTAB.), DR. M.SC. (TOKIO), HON. LITT.D. (PEKING), LL.D., SC.D., C.P.H., Director, National Quarantine Service, etc. Pp. 906; illustrated. Second Edition. Shanghai: National Quarantine Service, 1936. Price, $9.00.

AIMING to compose a history both of "the theory and practice of the twice-honored native art" of Chinese medicine and also of Chinese progress in modern medical science, the authors have really produced 2 books that necessarily vary greatly in content and form of treatment, even though it is maintained that Chinese medicine to be appreciated must be studied as one whole. The first quarter of the volume, by the medical historian, K. C. Wong, presents a panorama from "mythical times up to the close of the 18th century"; while the larger portion by Wu Lien-Teh, gives in considerable detail an account of the progress in China of occidental medicine in the past 230 years. One rather unfortunate sign of this fission is the appearance at the end of Book I of a chronological table that runs to A.D. 1887 with a second table at the end of Book II beginning with 1803. Significant of the form of treatment is that the first of these tables occupies 3½ pages, the latter 37. In the middle of the volume, too, are found useful lists of the Chinese dynasties and of important Chinese medical books.

To the ordinary reader, Book I will doubtless prove the more attractive. The most ancient of existing civilizations, China had her minstrels "celebrating her ancient heroes, whose tombs had already been with them for nearly 13 centuries," when in Europe our first poet "'Omer smote 'is bloomin' lyre." Starting with Fu Hsi, the legendary founder of the Chinese nation who lived about 2600 B.C., recorded Chinese medicine begins with his Pa Kua (Eight Diagrams), on which was founded Chinese medical philosophy, including the famous Yang and Yin (male and female) principles. The second of the mythical medical trinity, Shen Nung, is said by Wong and Wu to have reigned from 2838–2698 B.C., a truly heroic assignment that is less acceptable than Morse's figures, 2767–2687. Especially a student of drugs and poisons, Shen was known as the Father of Medicine and is still worshipped by the native drug dealers as their patron god. To Huang Ti, the 3d member of the Trinity, born the year of Shen Nung's death, is ascribed, with dubious historical support, the Nei Ching (Internal Classic), the earliest and greatest of Chinese medical writings. In its 2 books are outlined the paths that Chinese medicine was to follow for 4½ millennia: Most important features are the workings of Yin and Yang, the five elements, the functions of the Five Viscera, the varieties of the Pulse and their significance, the principles, use and contraindication of Acupuncture, Fevers, Bloodletting. The book's already sophisticated subtleties were not a little complicated by the 49 commentaries that appeared of various intervals during the dynastic period. A high point in Chinese medicine was the Chou dynasty (1121–249 B.C.), the age of Confucius, Mencius and Lao Tse, especially productive in the fields of medical organization, hygiene and public health. Another was the Han dynasty (B.C 206–A.D. 220), in which appear 3 of the greatest names of Chinese medicine, Ts'ang Kung, Chang Chung Ching and Hua T'o (the Chinese Hippocrates), the father of surgery and discoverer of anesthesia (an effervescent powder). These and the trinity previously mentioned constitute the chief gods of medicine in China today. In the T'ang dynasty (619–907) Chinese medicine is said to have reached its zenith. Seven specialties were recognized, and 4 kinds of doctors (physicians, acupuncturists, masseurs, and

exorcists). Drugs were divided into 10 main classes according to their action. Progress was still possible, though necrotizing rigidity had begun. Especially in the last 2 dynasties (Ming and Ch'ing) is the sterile decline apparent. Medical schools vanished, except for the one at Peking, and this was restricted to training the physicians for the Imperial family. Literally, any one could put up a sign and practice and there was no government supervision. Even the literati became subdivided into many cliques and exerted less and less influence in the country at large. Dr. Wong is able to add many life-giving details to this bare skeleton. Interesting accounts of the opium evil and of castration (including amputation of the penis) are found in the sections on cultural conditions and on surgery. Among the famous ancient drugs described are accounts of ginseng, chaulmoogra oil and ephedrine.

The story of smallpox prophylaxis is divided between both books—the use of inoculation about 1000 A.D. (Sung dynasty) appearing in Book I; while to vaccination introduced by Alex Pearson within a few years of Jenner's discovery is given a whole chapter in Book II.

The first book inevitably invites comparison with Morse's volume in the Clio Medica series, which though much smaller covers the same period. In the comparison neither suffers, as both are obviously written by men thoroughly conversant with their subject. The same topics are regarded as fundamental by both and facts are rarely contradictory. The Yang and Yin theory, the Gods of Medicine and acupuncture may be treated at greater length in the Clio volume; but this is more than counterbalanced by the more detailed treatment that the bigger volume permits of such topics as ancient medical drugs, medicine under the various dynasties, the early history of leprosy, beri-beri, cholera, smallpox and syphilis. Both books carry illustrations of the important medical Gods, both from authentic sources and yet as different as black is from white.

This Book I paints an interesting and instructive picture; yet, as the author points out, we must agree with Mencius, "It is better not to have the *Book of History* if we believe everything in it."

Dr. Wu's book on the "Introduction and Development of Modern Medicine in China" not only should serve its purpose of demonstrating to students of the old school that medical science "has not remained stationary since the time of Hua T'o"; but also forms a permanent and extremely valuable, detailed record of the various steps by which modern medicine gained its foothold in this most conservative of countries. The form of treatment is mostly chronological, 11 of the 15 chapters being given to the periods between 1820 and 1927. For each period, and some do not exceed 5 years, leading attributes are selected, such as: Introduction of western methods, progress in medical education, the spread of bubonic plague in 1894, and pneumonic plague in 1910, public health work, foundation of hospitals and medical schools, medical journals (both in Chinese and foreign languages), and the final period (1928–1936), consolidation under government auspices (98 pages).

The distinguished author, now head of the National Quarantine Service, is pardonably, and we hope legitimately, proud of the great advances made in public health, especially since the establishment of a National Ministry of Health in 1928. Grateful for the stimulus and actual help that has come from outside, he properly emphasizes the predominant achievement of the Chinese themselves. Though recognizing the vast fields still to be conquered (China, for instance, has 800,000 persons per hospital as against India's 42,700, Japan's 33,500, and the United States' 18,171), Chinese leaders are not sacrificing quality to quantity and are confidently proceeding with their policy of intensive medical progress. The activities are by no means limited to the coastal centers with which foreigners are familiar: Rural and county health centers have been established in 10 of the score or more of Chinese provinces, midwifery schools in 11, leprosaria in 11, over

6000 modern trained physicians are known to be spread over 10 provinces, while 426 hospitals were listed in 1934 in 20 provinces. Yet we may not forget that this is China; on page 448 we read: "Yuan crowned himself Emperor on December 13, 1915, but owing to growing opposition, fell sick and died in 100 days."

Statistics furnish tedious reading; yet one cannot have such a documented, detailed record as this without them; also the mass of detail included has necessarily resulted in a presentation rather than a narrative. For the very casual reader who does not wish even to browse through the text, the final chapter will summarize what it is all about. For the historical student, whether of the romantic, far distant past or of the active present, the whole volume will serve as a treasure house of reliable information. The new spirit of China, exemplified for the author in Sun Yat Sen and the Kuomintang, certainly appears to have achieved noteworthy progress in the field of health. Let us hope that it will be preserved by a similar progress along political lines!

We have devoted an unusually large space to this review both because the first edition was not "noticed" in this department and to demonstrate the importance of a work that must remain for a long time the classic in its field. E. K.

THE STORY OF LIVING THINGS. A Short Account of the Evolution of the Biological Sciences. By CHARLES SINGER. Pp. 572; 194 illustrations. New York: Harper & Brothers, 1931. Price, $3.00.

Two points stand out in this book: first, that though he is a historian, the author, like Ovid, rejoices in his own times and utilizes the past to illuminate the present; and second, that in spite of the progress of biologic specialization, it is possible to include within a book of medium size a scholarly and mature consideration of the problems of biology as a whole. Far different from the ordinary Introduction to Biology, this book achieves an adequate critical survey in simple concise terms, because, as the author himself suggests, "It is not the positive conquests of science that are peculiarly obscure, but rather the confused yet active battle-front along which science is advancing at any given moment."

The arrangement of the book is semi-chronologic. Part I carries the story of Biology from Aristotle through Harvey. Part II lays the basis for modern biology in sections on Inductive Philosophy, Classificatory Systems, Comparative Methods (Naturphilosophie), geographical and geological distribution, and evolution. The final Part selects 7 topics as the main themes of contemporary biology: the Cell, Vital Activity, Relativity of Functions, Biogenesis, Ontogenesis, Sex, Heredity.

Dr. Singer's fitness for such a task is unquestioned. Again he has demonstrated not only his familiarity with the various branches of biological science; but, much more, his ability to penetrate to the kernel of the matter, evolve thought-stimulating sequences and present a story sufficiently simple and leavened with personalities to carry along the serious reader entertainingly as well as profitably. E. K.

AN INTRODUCTION TO PSYCHOLOGICAL MEDICINE. By R. G. GORDON, M.D., D.Sc., F.R.C.P. (ED.), Physician to Royal United Hospital, Bath; Physician to Bath and Wessex Orthopædic Hospital, Bath, etc., N. G. HARRIS, M.D., B.S. (LOND.), D.P.M., Physician in Charge to Woodside Hospital; Physician for Psychological Medicine, Middlesex Hospital, etc., and J. R. REES, M.A., M.D., D.P.H. (CAMB.), Medical Director, Institute of Medical Psychology. Pp. 386; illustrated. New York: Oxford University Press, 1936. Price, $4.00.

WRITTEN as a text-book for the use of medical students, this work on psychiatry has certain interesting and commendable features. The first

70 pages are devoted to a brief survey of the field of psychology, especially in its relation to psychiatry. The workings of the diseased mind are the better appreciated by him who also has an understanding of the functioning of the normal mind, a knowledge of psychology which most texts in psychiatry take for granted. The next 60 pages take up the general principles of psychopathology and the psychopathology of common symptoms; this section is particularly well handled. Then follow the descriptions of the various mental disorders, with sections on the psychoneuroses, the psychoses, mental deficiency. The last two have valuable discussions of the legal aspects and the laws (British) relating to mental disorders. Since the treatment of mental illness is a subject for postgraduate study, no details of elaborate psychotherapeutic measures have been included, but the principles of treatment are adequately given. The presentation of the material is sound and the book is well written. R. K.

PATHOLOGIE DER FUNKTIONEN UND REGULATIONEN. By PROF. DR. L. LICHTWITZ, Chef der medizinischen Abteilung des Montefiore Hospital, New York; Clinical Professor of Medicine, Columbia University, New York. Pp. 332; 65 illustrations and 61 charts. Leyden: A. W. Sijthoff's Uitgeversmaatschappij, N.V., 1936. Price, Paper, holl. fl. 13.25; Bound, holl. fl. 14.50.

THESE essays by a distinguished internist cover a wide range of medical interests. They deal particularly with the disorders of internal secretion and the part played by the autonomic nerve system in the regulation and integration of the functions of the several organs in health and in disease. As the author himself states his is not a textbook or a work of reference but rather an illustration, through the discussion of many examples, of a particular mode of thought and method of investigation. There are chapters on the vegetative system and on general endocrinology, on the regulation of blood sugar and on hypoglycemia, on renal diabetes, on the pathology of the defense mechanism (inflammatory and immune reactions), on water metabolism, diseases of the joints and of the skeleton, on gout, on disturbance fat metabolism, on function and destruction of erythrocytes, diseases of the blood, hypertension, angiospastic diseases, visceral neuroses, functional pathology of the liver, nephritis, nephrosis, and the kidney of pregnancy, on age and senescence. All of these are worth reading, for they reflect the studies and experience of a medical investigator who obviously is both an optimist and a skeptic, qualities which the author believes should be among the chief characteristics of the physician. The excellent photographs, many of them of patients, add much to the value and enjoyment of this book. B. L.

ELECTRICAL SIGNS OF NERVOUS ACTIVITY. By JOSEPH ERLANGER, Professor of Physiology, Washington University, and HERBERT S. GASSER, Director, The Rockefeller Institute for Medical Research. Pp. 221; 113 illustrations. Philadelphia: University of Pennsylvania Press. London: Humphrey Milford; Oxford University Press, 1937. Price, $3.50.

THE present monograph embodies the third series of lectures delivered under the auspices of the Johnson Foundation for Research in Medical Physics. Like its immediate predecessor "it bears witness to the influence that developments in the fundamental sciences exert upon trends and progress in physiology. For it will become evident that but for contributions made by physicists in the field of vacuum-tube methods, which in turn rest upon experiments still more fundamental, on the theory and the production of electromagnetic waves, neither of these series of lectures would have

been possible." The studies discussed deal with: The analysis of the compound action potential of nerve; the comparative physiological characteristics of nerve fibers; some reactions of nerve fibers to electrical stimulation; sequence of potential changes; the excitability cycle. The lectures have admirably succeeded in demonstrating the applicability of physical methods to biological and medical problems. If for no other reason, the general medical reader will find this monograph of great interest; for the modern student of neurology the narrative of achievements, which would have been impossible but a few years ago, will be a source of inspiration and stimulation to "go and do likewise." B. L.

NEW BOOKS.

Clinical Parasitology. By CHARLES FRANKLIN CRAIG, M.D., M.A. (HON.), F.A.C.S., F.A.C.P., Col. U. S. Army (Retired), D.S.M., Professor of Tropical Medicine in the Tulane University of Louisiana, New Orleans, and ERNEST CARROLL FAUST, M.A., PH.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 733; 243 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $8.50.

Clinical Allergy. By LOUIS TUFT, M.D., Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital; Associate in Immunology, Temple University School of Medicine; Director of Laboratories, Pennsylvania Department of Health, Philadelphia. Introduction by JOHN A. KOLMER, M.D., DR.P.H., D.SC., LL.D., L.H.D., Professor of Medicine, Temple University; Director of Research, Institute of Cutaneous Medicine, Philadelphia. Pp. 711; 82 illustrations. Philadelphia: W. B. Saunders Company, 1937. Price, $8.00.

The Principles and Practice of Clinical Psychiatry. By MORRIS BRAUDE, M.D., Associate Clinical Professor of Psychiatry, Rush Medical College, The University of Chicago; Attending Psychiatrist, Cook County Psychopathic Hospital, Chicago. Pp. 382; 7 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $4.00.

A Brief Rule to Guide the Common-people of New England How to Order Themselves and Theirs in the Small Pocks, or Measels. [First published in 1677/8, reprinted in 1702 and 1721–22.] By THOMAS THACHER. Facsimile Reproductions of the Three Known Editions with an Introductory Note by HENRY R. VIETS, M.D. Pp. 54; illustrated. Price, $1.50.

A Discourse upon the Institution of Medical Schools in America. [Reprinted from the first edition, Philadelphia, 1765.] By JOHN MORGAN. With an Introduction by ABRAHAM FLEXNER. Pp. 63; 1 illustration. Price, $2.00.

Adaptation in Pathological Processes. [Reprinted from Transactions of the Congress of American Physicians and Surgeons, 1879, fol. IV, pp. 284–310.] By WILLIAM H. WELCH, M.D., LL.D. With an Introduction by DR. SIMON FLEXNER. Pp. 58; 1 illustration. Price, $1.50.

The above 3 books, (Publications of the Institute of the History of Medicine, The Johns Hopkins University, Fourth Series, Bibliotheca Medica Americana, Vols. I, II, and III, respectively.) Baltimore: The Johns Hopkins Press, 1937.

The Cost of Adequate Medical Care. By SAMUEL BRADBURY, M.D. Pp. 86; 13 tables. Chicago: The University of Chicago Press, 1937. Price, $1.00.

Obstetric and Gynecologic Nursing. By FREDERICK H. FALLS, M.S., M.D., F.A.C.S., Professor of Obstetrics and Gynecology, University of Illinois,

College of Medicine; Attending Gynecologist of the Illinois Research and Educational and Cook County Hospitals, etc., and JANE R. MCLAUGHLIN, B.A., R.N., Superviser of the Department of Obstetrics and Gynecology, Research and Educational Hospital, University of Illinois, College of Medicine; Instructor in Department of Obstetrics, University of Illinois, College of Medicine. Pp. 492; 83 illustrations (by Charlotte S. Holt). St. Louis: The C. V. Mosby Company, 1937. Price, $3.00.

Induced Inflammation of the Nasal Mucosa as Preparation for the Experimental Active Immunization Against Poliomyelitis Virus. By S. PESKIND, B.S., M.D., Cleveland, Ohio. Pp. 8. Cleveland: S. P. Mount Printing Company, 1937. (Price not given.)

Clinical Endocrinology. By SAMUEL A. LOEWENBURG, M.D., F.A.C.P., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia; Assistant Visiting Physician, Philadelphia General and North Liberties Hospitals, and Eagleville Sanatorium for Consumptives, etc. Foreword by HOBART A. REIMANN, M.D., Professor of Medicine and Clinical Medicine, Jefferson Medical College, Philadelphia. Pp. 825; 184 illustrations, 37 charts and tables. Philadelphia: F. A. Davis Company, 1937. Price, $8.00.

The Traffic in Health. By CHARLES SOLOMON, M.D., Assistant Clinical Professor of Medicine, Long Island College of Medicine; Lecturer in Materia Medica, Training School for Nurses, Jewish Hospital of Brooklyn. Pp. 393. New York: Navarre Publishing Company, 1937. Price, $2.75.

Condition Satisfactory. A Physician's Report of His Own Illness. By DR. SÁNDOR PUDER. Translated from the German by HILDEGARD NAGEL. With a Foreword by FRIGYES KARINTHY. Pp. 201. New York: ALFRED A. KNOPF, 1937. Price, $2.00.

The Harvey Lectures, Series XXXII. Delivered under the Auspices of The Harvey Society of New York, 1936–1937. Under the Patronage of the New York Academy of Medicine. By DRS. WILDER PENFIELD, EUGENE M. LANDIS, W. WALTER RANSON, R. SCHOENHEIMER, THORVALD MADSEN, HERBERT S. GASSER, C. N. H. LONG and SIR HENRY DALE. Pp. 245; illustrated. Baltimore: The Williams & Wilkins Company, 1937.

The usual high standard of this publication is maintained in the present volume by the following authorities: W. Penfield, "The Cerebral Cortex and Consciousness;" E. M. Landis, "The Passage of Fluid through the Capillary Wall;" S. W. Ranson, "Some Functions of the Hypothalamus;" R. Schoenheimer, "The Investigation of Intermediary Metabolism with the Aid of Heavy Hydrogen;" T. Madsen, "The Scientific Work of the Health Organization of the League of Nations;" H. S. Gasser, "The Control of Excitation in the Nervous System;" C. N. H. Long, "The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes;" Sir H. Dale, "Transmission of Nervous Effects by Acetylcholine." E. K.

Tumors of the Nervous System. An Investigation of the Most Recent Advances. The Proceedings of the Association, New York, December 27 and 28, 1935. (Association for Research in Nervous and Mental Disease, Vol. XVI of a Series of Research Publications.) Editorial Board: EDWIN G. ZABRISKIE, ANGUS M. FRANTZ, CLARENCE C. HARE. Pp. 394; 213 illustrations and 64 tables. Baltimore: The Williams & Wilkins Company, 1937. Price, $7.50.

The Medical Clinics of North America, Vol. 21, No. 4 (Philadelphia Number, July, 1937). Pp. 315; 11 illustrations. Philadelphia: W. B. Saunders Company, 1937.

In this Philadelphia number, the most important feature is the 9-article symposium on cardiovascular disease. The 14 other articles range from the recondite essential pentosuria to the (*horribile dictu*) "acute abdomen." As usual, much sound clinical information is to be found within the covers of this number. E. K.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By FRANK R. FORD, M.D., Associate Professor of Neurology, The Johns Hopkins University. Pp. 953; 107 illustrations, 14 charts and 14 tables. Springfield, Ill.: Charles C Thomas, 1937. Price, $8.50.

NEW EDITIONS.

An Introduction to Dermatology. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Dermatology, University of Kansas School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., L.R.C.P. (EDIN.), Instructor in Dermatology, University of Kansas School of Medicine. Pp. 666; 229 illustrations. Third Edition. St. Louis: The C. V. Mosby Company, 1937. Price, $5.00.

The third edition of Sutton and Sutton has been expanded by 45 new illustrations and brief descriptions of 35 previously undiscussed dermatoses. Hence it emerges as an increasingly authoritative and valuable guide to present day dermatology for the practitioner and medical student. An attempt at reclassification has been made in keeping with the newer etiologic and functional viewpoint in dermatology. One misses a bibliography, although much of the pertinent literature is well covered in the discussion. The book can be thoroughly recommended as an up to date, readable and highly practical presentation of the subject. V. G.

Manual of the Diseases of the Eye for Students and General Practitioners. By CHARLES H. MAY, M.D., Consulting Ophthalmologist to Bellevue, Mt. Sinai and French Hospitals, New York, etc. Pp. 498; 376 illustrations including 26 plates with 78 colored figures. Fifth Edition, revised with the assistance of CHARLES A. PERERA, M.D., Instructor in Ophthalmology, College of Physicians and Surgeons, Medical Department of Columbia University, New York. Baltimore: William Wood & Co., 1937. Price, $4.00.

This excellent manual continues to be the most popular text for medical students in their course in ophthalmology. The fifteenth edition has been carefully and thoroughly revised and brought up to date to include such recent subjects as dinitrophenol cataract, inclusion body conjunctivitis, gonioscopy, polaroid glasses, etc. F. A.

Treatment by Diet. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago. Pp. 642; 8 illustrations. Third Edition, revised. Philadelphia: J. B. Lippincott Company, 1937. Price, $5.00.

Rose and Carless Manual of Surgery. American Fifteenth Edition Edited by WILLIAM T. COUGHLIN, B.S., M.D., F.A.C.S., Professor of Surgery and Director of the Department of Surgery, St. Louis University School of Medicine; Surgeon-in-Chief, St. Mary's Group of Hospitals, St. Louis. From the Fifteenth English Edition by CECIL P. G. WAKELEY, D.Sc. (LOND.), F.R.C.S. (ENG.), F.R.S. (EDIN.), Senior Surgeon, King's College Hospital, etc., and JOHN B. HUNTER, M.C., M.CHIR. (CANTAB.), F.R.C.S. (ENG.), Surgeon, King's College Hospital, etc. Pp. 1586; 900 illustrations and 26 plates (18 in color). Baltimore: William Wood & Co., 1937. Price, $9.00.

Disorders of the Blood. Diagnosis, Pathology, Treatment and Technique. By LIONEL E. H. WHITBY, G.V.O., M.C., M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), D.P.H., Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital, and Pathologist, The Children's Hospital, Hampstead, and C. J. C. BRITTON, M.D. (NEW ZEALAND), D.P.H., Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital; Late Assistant Pathologist, Christchurch Hospital, New Zealand. Pp. 582; 60 illustrations, 12 plates (8 colored), and 15 tables. Second Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $7.50 with washable cloth cover.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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HYSTERECTOMY.

For many years there have been discussions among gynecologists relative to the type of operation which should be performed in a patient in whom removal of the uterus is indicated. The aspects of the question which are most frequently argued are: 1, should the abdominal or the vaginal route be employed? 2, if the abdominal route is selected, should the operation consist of removal of the entire uterus or only the supracervical portion, commonly called the subtotal or supravaginal operation? 3, should the ovaries be retained or removed in the cases where they appear grossly normal? 4, in the cases where the cervix is not removed, what is the danger of the later development of cancer in this retained stump? It is not the purpose of a review of this kind to answer these questions, indeed it would be quite impossible for any reviewer to answer them to the satisfaction of everybody interested in these questions. Therefore we shall present abstracts of recent literature pertaining to the subject and allow the reader to decide on which side of the fence he prefers to be.

Abdominal Hysterectomy. In the opinion of Richardson,[12a] the most cogent argument offered in support of the contention by the advocates of routine total hysterectomy is the apparent steadily mounting incidence of cervical stump cancer. In his own experience the occurrence of stump cancer is so rare as to be a negligible factor, but he cannot ignore the numerous reports of its occurrence in the experience of others. It is impossible to determine accurately its true incidence because no one knows how many thousands of subtotal hysterectomies have been performed throughout the world, but he does not believe that it exceeds 3%. In his opinion subtotal hysterectomy is indicated in only four types of cases: 1, those women requiring hysterectomy for benign disease who possess perfectly normal cervices; 2, cases in which the operative hazard compels the execution of rapid and conservative surgery; 3, a few cases in which for good and sufficient reason it is of paramount importance to preserve the function of menstruation; and 4, most cases requiring hysterectomy during pregnancy. Before decid-

ing upon subtotal hysterectomy, the surgeon should scrutinize the cervix with particular care, freely utilizing such diagnostic aids as the Schiller test, colposcope and biopsy, when in doubt as to the condition of the epithelium on its surface. Furthermore, remembering how frequently coëxisting carcinoma at and above the level of the internal os is overlooked, as soon as the body of the uterus is removed by the subtotal operation, it should be laid wide open so as to permit of accurate inspection of all the endometrium; likewise all fibroid tumors should be bisected and examined and an immediate frozen section should be made of any suspicious area. He believes that there is little likelihood that stump cancer will later develop in any cervix which survives the rigid application of these tests. Although Richardson is thoroughly skilled in all types of hysterectomy and has devised a very efficient technique for the complete operation, he is unbiased and states that the complete hysterectomy is a surgical procedure of far greater magnitude, requiring larger experience and more highly developed technical skill for its successful application than does the subtotal operation.

Read and Bell[11] studied a series of 2344 consecutive hysterectomies at the Chelsea Hospital for Women in England which were performed for various indications by 14 gynecologists. Of this series about 75% were of the supravaginal type and 25% were total operations. In the subtotal group the morbidity was 20.6% and the mortality was 2.1%, while in the group comprising total hysterectomies the morbidity was 27.1% and the mortality was 3.1%. After carefully tabulating their studies they conclude that each of the two types of operation has a definite place in gynecologic surgery. While the morbidity and the mortality are higher for the total operation, the sequelæ following the subtotal operation are more numerous and of more serious consequence than those following the total operation. Taking into consideration the remote deaths due to these sequelæ, the remote mortality rate of the subtotal operation is appreciably raised. The majority of the remote sequelæ could have been anticipated by a more accurate investigation of the cervix before operating and by the more frequent employment of exploratory curettage to rule out malignant disease. The remote complications encountered after the subtotal operation include cervicitis, cancer of the retained stump, cervical menstruation, prolapse of the cervix, cervical fibroids and intestinal obstruction. Pulmonary embolism especially follows the subtotal operation and accounts for a considerable proportion of the deaths. The more general employment of postoperative massage and exercises might diminish the incidence of this complication. In the total operation the use of silk in the neighborhood of the vaginal vault incurs a definite risk of sinus formation. These authors do not advocate the routine use of the total operation but feel that the scope of the subtotal operation is distinctly limited, since few women who have borne children have completely healthy cervices.

The opinion which Goodall[3] expresses is based upon a personal experience arising from 550 consecutive cases of hysterectomy about equally divided between the total and the subtotal operation. As his experience improved, the totals greatly outnumbered the subtotals, so that at present the former operation is selected in about 90% of the cases. It is not his intention to force the unskilled surgeon into an

operation graver than that for which he is fitted by experience. But to the skillful surgeon, to whom a slightly longer operation presents no greater deterrent than the extra time that is expended, the total hysterectomy will present great advantages to the patient. In brief, he lists the disadvantages of the total operation as the greater time required, greater skill required, greater blood loss, greater danger to vital organs, greater difficulty if the pelvic organs are fixed deeply in the pelvic cavity or if the patients are obese. On the other hand, the advantages of the total operation are fewer immediate postoperative complications, fewer remote sequelæ and smoother recoveries. When vaginal hemorrhage occurs after the total operation, as it has in slightly over 2% of his series, the vagina should at once be cleared of clots and packed gently with gauze by means of a uterine packer. To leave the vagina filled with clots is to invite further bleeding. In every instance the above procedure, preceded by a blood transfusion, has promptly arrested the bleeding. He has found that thrombophlebitis is three times as common in the subtotal operation as in the total and he ascribes this to the fact that it is due to an infection of low virulence and in the vast majority of cases it emanates from a mucosal disease.

In a series of 1376 abdominal hysterectomies presented by Siddall and Mack,[15] there were 1141 subtotal and 235 total operations with mortality rates of 2.6% and 6.4% respectively. In analyzing the series with regard to different operators with different degrees of skill, it was found that in every instance there was an advantage in mortality for the subtotal operation. Pelvic inflammatory disease made hysterectomy more dangerous and explained the higher mortality which occurred with removal of the adnexa. They believe that the danger of cancer developing in the cervical stump is not great enough to justify the additional risk of the total operation in any but a small proportion of cases. Other less dangerous procedures should be more frequently recommended. The cervix may be coned out from above at the time of the subtotal operation, but this will not remove the most frequent site of later carcinoma, namely the region of the external os. Of greater value is the removal of the cervix from below or cauterization of the cervix, either before or after the abdominal operation.

The removal of a myomatous uterus by *morcellation* is an old operation and was used to extract large growths through small incisions. The disadvantage of the procedure when practised in the orthodox manner was the increased bleeding which occurred as the tumor was delivered piecemeal. To overcome this objection Rubin[13] has developed what he terms "retrograde" abdominal hysterectomy with avascular morcellation. The operation is like the standard hysterectomy except that the pelvic blood supply is controlled with the large uterine tumor remaining within the abdomen. After ligation of the main vessels, the tumor is removed by morcellation through a small subumbilical incision, even though the tumor mass may extend up to the xiphoid. He believes that the smaller incision will prevent large hernias and, as the uterus is allowed to occupy its natural position during the operation, it acts as a non-irritating pad which prevents the intestine from prolapsing into the wound, lessening shock. In the event that any difficulty is encountered in the course of the operation on account of the small incision, it can readily be enlarged upward as far as desired.

The operation was devised and is recommended especially for the removal of the very large fibroids.

The question of whether a hysterectomy or a more conservative method should be used for the treatment of a perforated uterus has been considered by Ernst.[2] He reports 34 cases of perforation of the uterus complicating induction of labor or evacuation of the uterus after abortion, with 3 deaths or 9% mortality. In this series 3 cases were treated conservatively with no mortality, 1 case was treated by simple laparotomy with drainage and died, 8 cases were treated by suture of the perforation with no mortality and in 22 cases hysterectomy was performed with 2 deaths. Two of the 3 deaths in the series were in patients who came to operation with a well-established peritonitis, in 1 of which a hysterectomy with drainage was done, while the other was so hopelessly advanced that simple drainage was all that was attempted. Therefore, of the patients who did not have peritonitis at the time of operation only 1 was lost, or a mortality of 3% which, of course, is comparatively low. Although suture of the perforation is the operation of choice in the early cases, in this series hysterectomy was indicated 20 times because of the large size of the perforation, wounds of neighboring structures, unusual thinness of the uterine wall, infection, and the like. Only 1 of these cases died and that was due to a secondary hemorrhage from the ovarian artery.

Vaginal Hysterectomy. Although the great majority of gynecologists prefer to do hysterectomy by the abdominal route, those who prefer the vaginal route are usually quite expert in its performance, and in their hands this operation has a low mortality and can be applied in many complicated cases. Heaney[5] reports his series of 627 vaginal hysterectomies with 3 deaths, or a mortality of 0.47%. The indications for the operation were uterine fibroids in 338 cases, uncontrolled menorrhagia in 119 cases, uterine prolapse in 76, adenomyoma in 60 and for many other indications in the remainder of the series. The complication that is usually most feared is postoperative hemorrhage, but in this series there were only 5 cases. In 1 case it was necessary to perform a laparotomy and ligate a small vessel, 1 required vaginal suture, while the other 3 merely required vaginal tamponade. Adenomyoma of the rectovaginal septum is not infrequently associated with disease of the uterus requiring hysterectomy. This complication should not deter one from operating vaginally, for this growth is more amenable to attack by the vaginal route than by the abdominal. In one case of this sort a tiny perforation of the rectum was made which was immediately sutured with an uncomplicated convalescence. In 3 cases, at some time during the convalescence, the vaginal vault opened and a tube prolapsed and became adherent in the vaginal vault. In such cases the patients usually complain of a profuse watery discharge. When this occurs, slight traction is made on the tube under light anesthesia until it is completely delivered in the vagina, and then a ligature is passed around the tubal mesentery and the tube burned off with a light nasal cautery. Vaginal hysterectomy causes very little reaction to the patients, and Heaney states that there has never been reported a series of abdominal hysterectomies with so low a morbidity and mortality as he has reported in this series of vaginal operations.

The relative value of vaginal and abdominal hysterectomy for benign

uterine disease has been very ably presented by Richardson[12b] without assuming a partisan attitude for either one. Major abdominal operations of any kind are not usually well borne by the aged and infirm. In this group abdominal panhysterectomy involves genuine hazard, whereas the vaginal removal of the uterus is astonishingly well tolerated. In nulliparous women whose intrapelvic ligamentous and fascial supports of the reproductive, vesical and rectal units are normal, he always performs abdominal hysterectomy, unless there exists some specific contraindication to its use. Although adequate exposure for a vaginal operation in these cases may be obtained by the use of a unilateral or bilateral Schuchardt's pararectal incision, the bleeding from these incisions is always free, and a proper reconstruction of the divided structures is not always obtained. Even with the additional exposure obtained by these incisions the hysterectomy may still be difficult and hazardous in women with deep pelves and strong, unyielding uterine supports. Complicated pelvic lesions tremendously increase the technical difficulties. Therefore vaginal hysterectomy in the nullipara without uterine prolapse should be undertaken only by surgeons who have had large experience with the operation. As a general rule, total hysterectomy by either route should not be undertaken if there exists acute or subacute infection anywhere within the boundaries of the operative field. After the infection has subsided there are likely to be numerous adhesions which more or less fix the pelvic organs, and for this reason abdominal operation will be more satisfactory. If there are associated ovarian neoplasms it would seem wiser to employ the abdominal route so that there will be no spilling of ovarian contents and also that a thorough abdominal exploration may be made. While it is true that tumors as large as a 4 months' pregnancy can be removed by the vaginal route, it is not usually wise to do so when the tumor is larger than an 8 weeks' pregnancy. Caution should be exercised in delivering through the detached vaginal vault even a tumor of this size because of the danger of serious damage to the base of the bladder and its sphincter muscle from overstretching. If intraligamentary, retroperitoneal, cervical or subvesical myomas are to be dealt with, one should always assume that normal anatomical relationships in the true pelvis have become distorted. Frequently this occurs to an extraordinary degree and failure to recognize the added operative hazards thus produced is responsible for many divided ureters and bladder punctures. With regard to the treatment of uterine prolapse, he believes that where total hysterectomy is indicated for other reasons in conjunction with correction of the various types of vaginal hernia, the vaginal type of hysterectomy is to be preferred. He warns that operative attack upon hemorrhoids, fissure and fistula-in-ano, rectovaginal fistula, and complete laceration of the perineum should not be combined with total hysterectomy by either route. If removal of the uterus must antedate correction of such maladies, subtotal abdominal operation is much safer, because it evades the danger of contaminating the operative field with subsequent development of serious complications and also obviates the restrictions which such operations impose upon postoperative rectal therapy. He emphasizes the importance of a thorough surgical toilet of the vulva, vagina and cervix immediately preceding the operation, and states that a total hysterectomy should

never be performed by either route in the presence of any active infection. Even in the absence of active infection the vaginal flora and the cervical glands may harbor the most virulent types of streptococci, and failure to recognize this fact is responsible for an occasional fatality and for many instances of postoperative wound infections, secondary hemorrhage, pelvic cellulitis and other complications.

Ovarian Function After Hysterectomy. Arguments have frequently been presented for and against removing apparently normal ovaries at the time of hysterectomy. The conservatives feel that even though the uterus be removed, the ovaries serve an important function in the elaboration of internal secretions of much benefit to the patient. The radical school are of the opinion that following hysterectomy the ovaries soon become almost functionless and are a source of possible future trouble and hence should be removed at the primary operation. In order to throw some light on this subject some experimental work on animals was done by Burford and Diddle.[1] They performed total hysterectomy on 5 female monkeys (Macacus rhesus), including mature and immature animals, and noted the effect on the ovaries. The animals were followed for periods ranging from 121 to 217 days after operation. No impairment of ovarian activity could be detected by vaginal lavage studies, "sex skin" color records, or examination of the ovaries at laparotomy. A postmortem census of the follicles in the ovaries revealed no increase in follicular atresia for either the mature or the immature group. One immature animal went on to definite sexual maturity 103 days after hysterectomy. They conclude that hysterectomy in the Macacus rhesus monkey is without effect upon the ovary, except for purely traumatic effects. The monkey affords no evidence that the uterus contributes any endocrine influence upon the ovary.

This subject has been studied from the clinical aspect by Marx, Catchpole and McKennon,[7] who state that the contrast between the hormone picture and clinical symptoms after total and after subtotal hysterectomy is impressive and striking. In the majority of the total hysterectomies they observed a rapid increase in prolan and a less rapid decrease of estrin. Hot flushes occur almost immediately following the operation. Compared with this, cases of supravaginal hysterectomy show much less violent changes of the hormone picture, occurring more gradually and in the majority of cases appearing after several years and the hot flushes occur much less frequently and much later. Among 8 cases of total hysterectomy, they found 5 manifesting hot flushes of 6 showing an increase of prolan, whereas among 13 cases of supravaginal hysterectomy they found only 2 presenting hot flushes of 6 with a high prolan level. These findings indicate, first, that the increase of prolan is not necessarily associated with the production of hot flushes and, second, that with an equal rise of the prolan level, hot flushes are more apt to occur in cases of total hysterectomy than in cases of supravaginal hysterectomy. It seems that hot flushes are more likely to develop, the more abruptly the uterine function and the normal utero-ovarian-pituitary balance are disturbed, as it occurs in the total compared with the subtotal operation. They were surprised to find how long the ovary can continue to function after supravaginal hysterectomy since they found normal quantities of estrin in 2 women,

35 and 36 years old, more than 4 and 6 years after the operation, which would contradict the opinion of previous clinical observers that the life of the ovary after hysterectomy averages only 2 years. They believe that the preservation of only a small part of the uterus seems to have a retarding effect upon the appearance of retrogressive changes in the pituitary-ovarian function and the occurrence of menopausal symptoms. Their studies seem to support the theory that the uterus elaborates a catalytic principle acting upon some part of the pituitary-ovarian hormonal mechanism, regulating its normal balance and functional harmony. The amount of estrin output after hysterectomy is determined more by the biologic quality than by the amount of ovarian tissue retained.

A similar study has been made by Tamis,[16] who found that ovarian activity persisted longer in the women under 35 years of age at the time of operation than in the older group. Conservation of the ovaries in the younger group tended to retard the onset of flushes to a greater degree than in the older group, but in both groups, when they did occur, they lasted longer than when they appeared in the bilaterally oöphorectomized women. No direct relationship could be demonstrated between follicle hormone production *per se*, and the onset and severity of the vasomotor disturbances of the menopause. Whatever influence the ovary exerts over these disturbances is due to some other mechanism, in his opinion. It is believed by some that the endometrium produces a hormone and that the amount of flushes after hysterectomy is proportional to the amount of endometrial tissue excised. He therefore makes the suggestion that not only the ovaries be conserved when performing hysterectomy but also that as much of the uterine mucosa as possible be saved.

In a review of 2042 hysterectomies, Kretzschmar and Gardiner[6] found that complete removal of all ovarian tissue hastens the onset but does not shorten the duration of symptoms of the surgical menopause, as has been previously contended. The high incidence of menopausal symptoms following operations for pelvic inflammations would suggest that conservatism in this condition is unwise, if ovarian tissue showing degenerative changes is to be retained. The onset of the surgical menopause should not presuppose a decrease in, or a cessation of, sexual activity, since 57% of the patients in this series who developed hot flashes showed either an increase or no change in their libido.

Cancer of the Cervical Stump. The most potent, if not the only reason for advising the performance of total abdominal hysterectomy, is the possibility of the occurrence of cancer in the cervical stump which remains after the supravaginal operation. As stated earlier in this review, no one knows the exact incidence of this possibility, but the figures presented by Meigs[8] from the Massachusetts General Hospital are illuminating. There were 39,930 married women over the age of 30 admitted to the hospital wards for all reasons, from June, 1900, to June, 1933, and there were 751 patients with cancer of the cervix admitted in the same period. Thus in this population the incidence of cancer of the cervix is 1.8%. In the same 33 years there were 1774 subtotal hysterectomies for benign disease performed in the hospital, and in this period of time there were in the hospital but 13 cases of real stump cancer (0.73%). As this hospital receives patients from all

the New England states, and as many of the worst and most difficult problems reach there, it is reasonable to assume that it would admit more cancers of the cervical stump from other hospitals than it would lose following its own hysterectomies. This figure, 0.73%, is less than one-half of the percentage incidence of cancer of the cervix. In other words, cancer of the retained cervix is not more likely after subtotal hysterectomy than, but one-half as likely as in, women as a whole. For the advocates of total hysterectomy to maintain their position it would be necessary for them to show not over a 0.73% difference in mortality between subtotal and total hysterectomy. Meigs states that this might be accomplished by an operator well trained in this type of surgery, but to advocate total hysterectomy to all surgeons throughout the country in all patients to prevent the occurrence of cancer in the cervical stump would be the cause of far more deaths in an attempt to prevent cancer than would die of cancer itself. It is also obvious that total hysterectomy cannot be advocated in only special groups of cases, but it must be advocated in all, even those who have had no children. No one will deny that total hysterectomy is a more formidable and more serious operation than simple subtotal removal of the uterus. The morbidity, the chance of injuring the ureters and bladder, the possibility of vaginal prolapse and the foreshortening of the vagina in the young married woman are all against this operation as a routine.

In a series of 1900 cases of supravaginal hysterectomy at the Free Hospital for Women in Brookline, Pearse[10] estimates that the incidence of stump cancer is about 1%. In comparing the cases in which the operation was done for fibroids with those in which it was done for pelvic inflammatory disease, the incidence was about one-half as great in the former as in the latter. In no case of previous prolapse or procidentia did cancer occur in the retained stump. He is also of the opinion that unless the mortality from total hysterectomy can be shown to be the same as or less than that for supravaginal hysterectomy, the possibility of later cancer of the cervix should not be considered as an indication for complete extirpation.

As a result of their study of 38 cases of stump cancer examined at the Manchester Radium Institute, Nuttall and Todd[9] classify these cases into 2 groups: Group A consists of coincident carcinoma which was present at the time of hysterectomy or discovered within such time as to justify the assumption that the growth was then present. Group B includes the true stump cancers which were discovered 2 or more years after the hysterectomy. The prognosis varies with the groups. In Group B it is relatively good, being at least the equivalent of that of ordinary cancer of the cervix. In the first group it is very bad. The generally accepted view that the prognosis is poor arises from the consideration of the 2 groups as a single entity. The good results obtained in true stump cancer do not support the contention that subtotal hysterectomy should be abandoned because of the risk of subsequent malignant change in the stump. The bad results obtained in coincident carcinoma are analogous to those obtained following any incomplete operation elsewhere in the presence of malignancy. They are the result of missed diagnosis and emphasize the importance of careful pre-operative examination.

In the series of over 500 cases of supravaginal hysterectomy which

Scheffey[14] reports, the incidence of the later development of cancer of the cervical stump is calculated as 0.902%. He stresses the importance of pre-operative treatment of the cervix and shows that of 170 patients who had such treatment only 1 developed stump cancer, an incidence of 0.508%. On the other hand, of 384 patients who received no cervical treatment prior to supravaginal hysterectomy, stump cancer developed in 4, an incidence of 1.04%, or twice that which occurred in the other group. When stump cancer develops, it should be treated by irradiation, using both radium and Roentgen ray. He reports a series of 10 cases, 4 treated with radium alone, 5 with radium and Roentgen ray and 1 with Roentgen ray alone. Three of these are alive and well 8 years after treatment, representing a 5-year salvage of 42%. One is alive and well 4 years after treatment and 1 is alive and well after 2 years. Considering the entire group, this represents a present-day salvage of 50%, which is certainly a very creditable report.

Healy and Arneson,[4] in discussing a series of 67 cases of stump cancer seen at the Memorial Hospital, New York, also agree with the previous authors that the low incidence of stump cancer does not justify routine total hysterectomy. These cases have been treated by irradiation with a 5-year salvage of 14%.

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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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PUBLIC HEALTH PROBLEMS: METHODS AND POLICY IN THE CONTROL OF SYPHILIS.

THE control of venereal ("genito-infectious" [24c, 27b.c.e]) disease, and of syphilis especially, has long had passive recognition at the hands of public health authorities as one of the major disease problems of the

world. Within the past decade a wave of interest has been gathering headway and has been brought to a crest with the appointment as Surgeon-General of the United States Public Health Service of Dr. Thomas Parran, Jr. It is Dr. Parran's evident intention to give to the problem of syphilis during the next decade or longer a very substantial share of the energies devoted to public health in this country. An orientation with respect to the problem and its bearings on medical practice is, therefore, timely and important.

The foundation for any program of such importance is an adequate study of prevalence, and this the United States Public Health Service has been developing in this field, with the coöperation of other agencies such as the American Social Hygiene Association. The most authoritative recent review of this work is that presented by Dr. R. A. Vonderlehr,[47b] in charge of the Division of Venereal Diseases, U.S.P.H.S., at the December Conference on Venereal Disease Control, Washington, December 28–30, 1936. On the basis of one-day cross sections and other statistical determinations, it is now definitely known that the minimum number of persons in the United States constantly in need of medical care because of syphilis is 683,000, or 4 per 1000 population.[45] Annually in the United States one-half million cases of early syphilis seek authorized medical care.[47b] There is a large though undetermined number of individuals acquiring the infection who neglect treatment until some late manifestation forces them to have attention. As Vonderlehr points out, the disease is never thought of as epidemic in the United States, yet annually there are twice as many new cases of syphilis as scarlet fever, 13 times as many as diphtheria, 28 times as many as typhoid, and $1\frac{1}{2}$ times as many as of tuberculosis. The attack rate for syphilis based on a New York State survey is $2\frac{1}{2}$ times as great in cities over 10,000 as in cities under 10,000, being 41.6 per 100,000 in the larger cities. The urban attack rate was 40% higher than that for upstate New York. Incomplete reports substantiate the statement that the incidence of the disease is highest in the South, owing to the presence of a large infected negro population. Analyses of the age, sex and marital status bring out conspicuously the youthfulness of those infected. It is estimated that 100,000 acquire the disease before 20, and even that 11,000 acquire it between the ages of 11 and 15. The incidence of syphilis in the colored race is twice that in the white, and twice as high in the single male as in the single female.[27f]

The trend of the disease in this country has been investigated as a significant guide to what will be required in its control. From 1919 to 1930 there has, of course, been a gradual increase in the rate of reported cases for the country as a whole.[46a] Special surveys have been made to avoid the obvious error of statistics based on mere increase in reported cases. From such one-day censuses in special communities aggregating $8\frac{1}{2}$ million in population, it is apparent that the prevalence rate of syphilis increased between 1927 and 1933, 3.4%. Between 1930 and 1934 in Massachusetts, it increased 1.5%, the rate for the female increasing 12 times that for the male.[27f] The morbidity surveys of upstate New York have shown an increase in the prevalence rate for all stages of syphilis of 32%.[47b]

In contrast to this general increase, surveys of special localities for early syphilis have shown such figures as a decrease of 13% between

1927 and 1933 in 17 selected communities,[45] a decrease of 31% between 1927 and 1935 in Massachusetts;[27f] and of 45% in upstate New York during the same period. This decline in early syphilis, as will be seen, is accepted throughout the world as one of the most usable and hopeful criteria of public health control for the infection. Late syphilis increased in the respective groups above mentioned 11%, 19% and 60%. Syphilis in pregnant women, on the other hand, offers a hopeful contrast with a striking decline in certain special areas such, for example, as the State of Massachusetts, in which Hinton's examination[27f] of the serologic reactions of nearly 8000 pregnant women between 1915 and 1919 and 17,000 pregnant women between 1930 and 1934 indicated a reduction of 70% in positive and 76% in doubtful serologic reactions in spite of the recent employment of much more sensitive tests for a 9 months' period in 1934. A review of stillbirths, in which syphilis is reported as the etiologic factor shows no decline between 1922 and 1933, but there is a decline in the general mortality of infants due to syphilis from 0.86 to 0.52 between 1921 and 1933.[44]

Cardiovascular syphilis, so far as available figures indicate, is showing a downward trend in spite of the upward trend of heart disease at adult ages in the general population. In 1914, at the Massachusetts General Hospital, 12% of a group of cardiac cases were due primarily to syphilis, while in 1928 the proportion due primarily or secondarily to syphilis was 5%.[50] A reduction of 20% has occurred in aneurysms in the same hospital,[5] and aortic insufficiency and aneurysm have dropped 40% in the United States Army in the 10 years ending 1934.

In the field of neurosyphilis, first admission rates for paresis in 500 institutions in the United States show no change from 1922 to 1933, while first admissions for other causes than paresis have increased 17%. In Massachusetts, a slow decline has been apparent for males since 1920. Mortality data for paresis in the registration area of 1900 indicated a decline from 1916 to 1933. In New York and Massachusetts, there has been a rapid decline from 1924 to 1927, but since 1928 the rate has remained stationary at 3.8 per 100,000 population. The death rate for tabes dorsalis declined from 3.0 in 1915 to 0.9 in 1933.[46b]

It is apparent then, that syphilis is a major, if not *the* major national health problem, that the disease itself is at least not on the decline in this country, though the incidence of early syphilis where public health measures are achieving some degree of success is definitely decreasing.

The Medical Situation. Controllability of Infectiousness and Prevention of Late Complications. A number of summaries of today's medical situation with respect to the disease, and particularly to that of control by prevention of infectiousness are available.[6,9,16,24b,29,40,41,47a] The inspiration to much of the work that has clarified and organized our conceptions on this matter should be traced to the Health Organization of the League of Nations, which in 1928 organized the Commission of Experts on Syphilis and Cognate Subjects which, under the chairmanship of Jadassohn, drew up a comprehensive scheme for international study of therapeutic methods and results in the early phase of the disease. From this, in its various national ramifications, sprang the inspiration for the Coöperative Clinical Group and the United States Public Health Service studies of American methods and results which today form the most tangible and dependable basis for American

practice side by side with their incorporation into the International Treatment Standard formulations of the League of Nations Commission. A convenient summary of the principles involved in the use of treatment for the control of syphilis is that of Moore (Chairman's Report in Proceedings of the Conference for Venereal Disease Control Work, Washington, D. C., December 28–30, 1936).[24a] As an indication of the source to which public health must turn for help in the treatment of the disease, it appears that 55% of the physicians engaged in private practice in this country do not treat syphilis at all. Slightly more than 50% of all patients known to have the disease are treated in clinics. Clinic treatment is in general better in quality than that given in private practice. In practically all communities in the country the demand on private practitioners for treatment should be increasing, but in spite of this, almost everywhere the facilities now available are unquestionably inadequate to meet the potential case load. Clinic practice in this country is at present estimated to be only 25% efficient, and for the potential case load only 10% efficient. It is felt, therefore, that the clinic rather than the private practitioner is the backbone of the community program for the control of syphilis. There need, however, be no conflict between clinic and private practice for there is easily enough for both. The major emphasis of clinic practice should be on the treatment of the patient with infectious early syphilis. Where the syphilis clinic is not part of a general hospital, expert consultation service should be developed, a need, indeed, which is felt throughout the entire field of public health and private management of the disease at the present day.

The amount and kind of treatment required to control syphilis as an infectious disease has been reviewed in the publications of the Coöperative Clinical Group[10a,b, 24e, 28, 43a] and is summarized by Stokes[40] and by Moore.[24a] Quoting Moore, the principles involved in the management of early syphilis presuppose that the average patient is a healthy young adult free from complicating diseases. The manifestations of syphilis are uniform in this type of patient and uniform results are achieved with a surprising regularity under standardized modes of procedure. The broad principles established by the Coöperative Clinical Group and United States Public Health Service studies and in the work of the League of Nations Commission of Experts are as follows: Results of treatment by two systems, the Danish-British Intermittent System and the American Continuous type of treatment are authoritatively established. For American practice the Continuous System is the more acceptable standard and presupposes in the management of the early infection no rest period of any kind until arsenical treatment is finished. Treatment must be prolonged for a minimum of 15 to 18 months regardless of serologic findings at the time the disease is diagnosed and regardless of serologic progress during the treatment. For the control of infectiousness a minimum of 20 injections each of an arsphenamine and a heavy metal (preferably bismuth) are essential. For the accomplishment of individual cure a minimum of 30 injections of an arsphenamine and 40 of a heavy metal are desirable. Lifelong post-treatment observation with periodic reëxamination has the support of many observers, but modifications of this requirement have

been suggested by the study of the question made by Stokes and Usilton.[41]

The system of treatment carrying out these principles which has been laid down by the United States Public Health Service as the basis of effective practice for this country is what is technically spoken of as the Continuous-Alternating technique. That is, the arsenical drug is given for a series ranging in the case of old arsphenamine (606) from 4 to 6 injections, and of neoarsphenamine (914) from 8 to 10 injections at weekly intervals, the first 2 or 3 injections being perhaps crowded into the first 10 to 15 days. Upon the completion of this arsphenamine course, or commencing simultaneously with the last injection or 2, the patient receives bismuth salicylate intramuscularly for a series of injections ranging from 4 to 6 at weekly intervals. The patient then resumes his arsenical for a second course, approximating in length the first course and again at its close receives bismuth exclusively for a period similar in length to that of the first bismuth course. Thus, courses of arsenical and bismuth alternate with or without overlapping until the patient has received the optimum of 30 injections, or more if any indications for prolongation of treatment have arisen (*c. g.*, fluctuating or weak positive serologic tests, symptomatic recurrence, and so forth). Following the completion of the arsenical and bismuth alternating phase of the treatment, the patient continues bismuth intramuscularly and for the first time in his course is allowed brief rest periods of 4 to 6 weeks between bismuth courses of 6 to 10 injections. When the patient has received a total of at least 30 arsenical injections and from 40 to 60 bismuth injections he is rated as ready for 2 years' probationary observation provided his course up to this point has been absolutely uneventful. An essential feature in the management of every case of early syphilis is the examination of the spinal fluid, which should be properly performed between the sixth and twelfth months of treatment and certainly before the first rest period is granted. It should be made clear to American practitioners that the continuous-alternating system just described is unquestionably superior to any of the American forms of intermittent treatment. Repeated studies[39b,40,43a] have demonstrated very clearly that the lapse, or rest period is in American practice responsible for drops in ultimate efficiency ("cures") ranging from 10 to 40%. The absolute curative efficiency of continuous-alternating treatment at the most favorable period of the disease, namely, the seronegative primary, is 86.4%. It seems probable in resurveys now in process that the absolute efficiency of this system of treatment will ultimately range in the 90's. Curiously enough it appears that the use of the continuous-alternating system of treatment in fully developed secondary syphilis yields better results than would ordinarily be expected; namely, 81.5%.

The influence of continuous-alternating treatment upon the incidence of infectious relapse has been repeatedly reviewed[40, 42, 43b] and need not be dealt with here beyond the statement that the continuous-alternating system above described has, in all particulars connected with relapse, an unmistakably higher efficiency rating than that of American types of intermittent and irregular treatment.

It is an aphorism to be dinned into the ears of the medical profession

by every possible device that late syphilis is the consequence of inadequately managed early syphilis. To this statement also the observations of the Coöperative Clinical Group have given statistical background. Cardiovascular syphilis,[10b,39b] for example, developed in 1.6% of 935 early syphilis patients followed from 3 to 10 years and in 6.7% of 105 patients observed from 10 to 20 years; but not one who had had adequate treatment for early syphilis developed a serious cardiovascular lesion in the 3- to 20-year group. A Coöperative Clinical Group survey of asymptomatic neurosyphilis, with O'Leary as spokesman,[28] demonstrates that adequate treatment given by the Continuous System results in the lowest incidence of neurosyphilis (11.7%) of any form of treatment now available. The ancient bugaboo of supposed predisposition to neurosyphilis by modern treatment methods has by this study as well as a number of others been embalmed for decent burial.

In no aspect of the transmission of syphilis has its controllability by adequate treatment been more fascinatingly or effectively demonstrated than in the field of congenital infection of the fetus. The treatment of the pregnant woman has revolutionized the situation for the child. The pioneer work of Boas and Gammeltoft[3] has found effective continuation in the demonstrations by McCord,[22] Bartholomew[2] and others in the United States of the striking protective value of treatment of the mother for the potentially syphilitic child. The principles, as understood today, are summarizable in terms of the time in the pregnancy when treatment is begun and the amount of treatment administered. The serologic state of the mother during the pregnancy also influences the outcome; a mother seronegative during pregnancy has an 81% prospect of a healthy child, while a mother seropositive during the pregnancy has only a 57% prospect of a healthy child.[10a, 39b] If treatment is begun before the fifth month the prospect of a healthy child aggregates 78% as compared with 61% if treatment is begun after the fifth month. If 10 arsenical injections and 10 heavy metal injections are given before the fifth month, 91% of the children are healthy. The preponderance of arsphenamine over heavy metal in the treatment scheme favors the birth of a healthy child. With reasonable attention to the established rules for the prevention of complications, the pregnant woman is an admirable subject for treatment and, in fact, tolerates it somewhat better than the non-pregnant woman. Regardless of serologic status there can be no question that the untreated syphilitic woman is a potential carrier of infection for the fetus up to 10 or 11 years after she acquires the disease. In fact, the untreated seronegative pregnant woman in the CCG statistics gave birth to only 28% healthy children.

It is apparent then, that treatment is the strong right arm of practically every aspect of the control of the disease today. To find the infected individual, to find him early, to treat him continuously by a combined arsenical and heavy metal therapy to an already established optimum standard is the essence of the matter.

The Control Setup With Its Possibilities and Limitations. To all students of the problem it is now apparent that if an arsphenamine can be brought to each infected individual in adequate amounts with regularity, our mastery of the disease can be all but complete. For the demonstration of this fact we are indebted not alone to the clinical observations of disappearance of Spirochæta pallida from infectious

lesions within 24 to 96 hours following a single injection, but to what might be regarded as public health laboratory experiments in the control of syphilis, of which the technique of the Scandinavian countries during the past half century has been the outstanding model and "health demonstration." The principles established by the Scandinavian type of organized attack on the disease have been admirably reviewed by the New York Commission, appointed to study various phases of continental experience.[8] It is important to understand both the application and limitations of the Scandinavian procedure, because they are now so widely used as an argument for the infallibility, one might say, of public health control of the disease. The Danish scheme in operation in many of its essentials since 1788, provides first, for the reporting of all cases of syphilis and gonorrhea, but not by name unless delinquent; free treatment (July, 1790); compulsory treatment (1874); legal prohibition of prostitution and solicitation (1906); and the assumption by the State of the entire cost of providing for the diagnosis and treatment of all cases of syphilis and gonorrhea (1932). Here, then, clearly outlined, is the skeleton framework upon which, as a public health issue, the control of syphilis must be built.

Some notion of the effectiveness of the Scandinavian program for the control of syphilis may be gained statistically from the incidence rates for the disease in three representative cities; in 1919 as compared with 1934. In the city of Copenhagen the rate fell from 527 to 28 per 100,000. In Stockholm, the rate declined from 450 to 7 per 100,000. In Oslo, the decline was from 350 to 30 per 100,000. Such figures as these which foreshadow a virtual extinction of the disease in the communities concerned constitute the basis for the prevailing optimistic statement in national antivenereal programs throughout the world.

It is important for the student of these questions, however, to realize that such results as these when examined from other angles are susceptible of varying explanations not necessarily associated with the effectiveness of a public health campaign. Moreover, it must be realized that in the Scandinavian countries highly special conditions prevail which can be reduplicated only with the greatest difficulty, if at all, through a large part of even the civilized world. A homogeneous population long accustomed to public health practice and with a medical profession thoroughly imbued with the disciplined conception and thoroughly equipped with the high standard of educational and practical accomplishment necessary for such a task inevitably constitutes a unique rather than a general demonstration of the possibilities before us. That it is possible, however, by even less ideal applications of the principles above set forth to bring about substantial reductions in the incidence of venereal disease, has been illustrated for our own state of Massachusetts which in many particulars reduplicates the special characteristics of the Scandinavian countries. In intelligence and intensiveness the movement against syphilis under Nelson's direction in this State achieves a high for American accomplishment today. Nelson[27f] finds that neurosyphilis in Massachusetts has sustained in 4 years an incidence reduction of 32.3%. This is confirmed in several directions. Syphilis in pregnant women in 15 years has been reduced 70%; admissions to syphilis clinics in 10 years in spite of an expanding program have been reduced 30%. The latest available statistical data from

New York State, whose program ranks with that of Massachusetts in effectiveness, very closely parallels the Massachusetts trend.[46a]

Whether the optimism engendered by these successful local programs can be justified in a national field is, of course, an important question for which the evidence in Great Britain is quite widely accepted as valid.

As a nationwide setup for the control of venereal disease, that of Great Britain has many features applicable to practice conditions in other larger countries, including the United States, and these should be summarized in order to add point to the figures indicative of the degree of their success.[8] The public health services of Great Britain are combined under a single central governmental agency, the Ministry of Health. The actual provision of facilities for control of the venereal disease situation is, however, local, through the County Councils and County-Borough Councils which, of course, recognizes the extremely important local phase of the control of this type of disease. The influence of the Ministry of Health, however, exerted through Colonel L. W. Harrison and conditioned by its larger share in the finance, is paramount. It has made possible the development of uniform high-grade free diagnostic laboratory service confined to approved laboratories throughout the United Kingdom, and control of placement and operation of clinics comparable to that possible in municipalities and smaller countries like the Scandinavian. The free distribution of drugs has served to indicate the partition of the existing treatable syphilis between private practitioners and public clinic agencies, and shows that only about one-sixth of all treatment conducted is carried on outside of government clinics. The profession at large may therefore be judged in Great Britain, practically to have surrendered the venereal disease problem except in a few of its special aspects, to the State. Three-fourths of the cost of treating venereal disease is borne by the central government which naturally makes the local authorities amenable in the highest degree to suggestion and coördinative advice. Something short of $2,500,000 is the approximate annual expenditure involved, which affords a species of measuring tape for what should be expected in larger countries like the United States.[12, 27d]. This is interpreted by Colonel Harrison as approximating 5 cents per capita per annum. It is a striking fact in British venereal disease practice that the reporting of venereal disease whether by name or number to central authorities and the use of any form of compulsion in the acceptance and continuance of treatment has thus far been avoided. The improvement in the control situation in Great Britain may, therefore, be interpreted as a product of education rather than force.

The number of cases of syphilis dealt with for the first time in treatment centers throughout England and Wales has been reduced from the peak of 1920, 42,805 cases, to 19,335 in 1935. This represents a 55% reduction and indicates that the volume of syphilis has declined within 15 years, since the peak, to 45% of the original figure. Cases of syphilis with infections of less than a year's duration have been reduced from an incidence rate of 2.28 per 10,000 population to 1.47 per 10,000 population in the 5-year period 1931–35. This is a reduction of 35%. The death rate from infantile congenital syphilis has been reduced 86% from the peak year in 1917 to the low of 1935.[1]

The Obstacles to Syphilis Control. The optimism inspired by the apparent logic of the situation, particularly as regards the chemotherapeutic control of infectiousness and the statistical evidence just cited from various sources, cannot be accepted without critical analysis. This was attempted by Stokes[39b] in a consideration of the obverse side of the picture. Pointing out a number of as yet unanswered problems concerning the Spirochæta pallida itself and the reservoir of infection in the asymptomatic carrier together with such considerations involving the granular form of the organism and possible relations to virus diseases, this author calls attention to the inconveniences and difficulties of dark-field diagnosis, which will probably require the development of a centralized mechanism, and the margins of uncertainty and error involved in serologic tests especially from the standpoint of their technical performance. He points out that the antisyphilis campaign from the standpoint of publicity and promises is proceeding far ahead of a rational expectancy for the development of adequate facilities. For example, the proposal to have a serologic test for syphilis become part of the examination of 7,700,000 annual admissions to medical and surgical beds as the first step in uncovering the infection in the population at large, is in itself an undertaking for which no large nation and certainly not the United States, is anything like prepared (*cf.* Moore[24d]). When, in addition, the total of out-patient and dispensary examinations is included; when it is estimated that 3,000,000 new syphilis patients annually will be uncovered, 650,000 of them fresh infections, it is apparent that the money and generalship alone required for this single phase of the enterprise will be very large. The lethargy of the physician where such routinization is involved, the attitude of the courts,[39b] and most recently, the inadequacies of the performances of laboratories themselves,[11] all gravely influence the future of this most important detective effort. While there has been a substantial increase in alertness, the great primary essential to the recognition of syphilis and the comprehension of its behavior in any and all phases, there is no question that the teaching of medical students and the knowledge of the general practitioner at the present time, both in diagnosis and in treatment are wholly inadequate to the responsibilities involved in the new campaign. The *terra incognita* of the woman's genital tract, the bearer of the large proportion of infectious lesions during the critical transmissible period is emphasized. Epidemiology with respect to syphilis is still in its infancy. There does not exist at the present time even the necessary trained personnel to undertake the difficult and exacting detective work of tracing the devious course of syphilis through the community. That such a personnel can be developed is a foregone conclusion, but the time involved will certainly not bring the control of syphilis and its extinction as a disease into the 30 years of an ordinary generation. The influence of money, vice and alcohol has by no means diminished in recent years, and much must be learned and relearned from studies of this problem whose titles are now all but forgotten in the literature. Female passive transmission of the infection; the extent and possible extension of perversion also bids fair to take its part in the final reckoning.

The treatment control situation contains intrinsic difficulties of which

enthusiasts often lose sight. The minimum treatment adequate to the control of infectiousness constitutes in reality not the magic wave of a wand as so often depicted, but a tedious, exacting, inconvenient, costly, sometimes dangerous procedure, demanding of the patient a more than average display of character, and of those who care for him an extraordinary knowledge and tact in dealing with human nature. Granted even that patients, actual and potential, can be educated to the point of maximum coöperation, there still lies before the venereal disease control movement a vista of educational effort directed at the medical profession itself for which present-day provision is wholly inadequate. Wile[51] has pointed out that 58 of 63 undergraduate medical schools surveyed in the United States make only the most skeleton and inadequate provision for instruction in syphilology, and Stokes and his coworkers at the University of Pennsylvania Clinic[33] have pointed out clearly how even minor technical slips in treatment given by supposedly skilled organizations act to break up the allegiance to treatment and the ability to continue it which is so vital a part of the present-day program. Prophylaxis, mechanical and chemical, has critical weaknesses inseparable from human nature itself which are too seldom considered by enthusiasts and which can be dealt with only by a fundamental reëducational program of the most comprehensive sort. The decline in the incidence of syphilis, while demonstrated by the figures previously cited, has flies in its ointment, too. It is by no means general throughout the world, and the existence of waves in the epidemiologic curve of syphilis have been pointed out by von Düring[49] and Gumpert,[15] and suggested by Källmark's[20] mathematical analysis. In spite of widespread educational effort, treatment for syphilis must be rated as substandard throughout the larger part of the world, and this has been already responsible for bringing to a standstill programs and prospects such as the Belgian, which seemed at the outset certain of success (Schwers[36]). The adverse influence of travel, of fluid population, of heterogeneity in language and race, and of the limited effectiveness over a period of years of publicizing educational method must all be rated as obstacles to be met and overcome. Modern sex life is for the moment frankly against the movement for the control of venereal disease. Fear itself, long an actual, though sometimes over-rated deterrent, is rapidly losing what influence it has had. Even the clinic, rated as the most powerful instrument in carrying through treatment prevention, has been repeatedly placed in a thoroughly unfavorable light. The international investigation by the League of Nations Commission of Experts disclosed inadequacies in diagnosis and treatment among the selected clinics of the world which were a shock from an unexpected source. The methods for separating the 18 to 20% of onsets of syphilis from their gonorrheal masks are still imperfect, not so much in themselves as in the practically total failure to apply serologic follow-up and adequate personal examination to the patient with the less distinguished venereal disease.[7] McKneely's[23] recent study of venereal disease clinics in this country is a devastating indictment, which should be read, and pondered and acted upon by the head and personnel of every venereal disease clinic in the world.

The American Program. It must be apparent then, that despite the intrinsically favorable situation, only the finest and most deter-

mined planning and action can make reality out of the enthusiastic hopes of many of the most distinguished personalities in this field. The American program, though heralded by a sudden puff of press enthusiasm and support as expansive as it was unexpected, is endeavoring to keep its feet on the ground and to proceed step by step to utilize the advantages and meet the difficulties above described.

Four factors promise to be of primary importance in the movement. The first of these, historically speaking, is the work of the Coöperative Clinical Group, stimulated by the International, or League of Nations Investigation, and carried forward in detailed studies with the aid of the United States Public Health Service statistical organization far beyond any other study of national scope. This work sets standards of practice never before available to the profession. In the 5 University Clinics of the Group* plus those of several collaborating agencies, a total material of approximately 75,000 cases has been gathered. Reports covering early syphilis [24a,b, 40, 41, 43a] (6807 cases), latent syphilis[24c] (1936 cases), syphilis in pregnancy[10a] (3817 cases), late prenatal syphilis[10c] (1010 cases), cardiovascular syphilis[10b] (10,614 cases), and preliminary studies of neurosyphilis[28] (5293 cases), are already in print, the collected papers constituting a massive large scale textbook of modern procedure in the diagnosis and treatment of the disease from the standpoint of American practice. Physicians whose interest has been stimulated by the public health authorities, and the general publicity attitudes towards the disease would be well advised to secure through the United States Public Health Service reprinted material from these studies as the most recent and authoritative statement of therapeutic ideals easily available to them. Under a permanent form of organization the Coöperative Clinical Group is continuing the effort to interpret into practical and usable terms the modern treatment of the disease including through the work of subcommittees the relative values of various methods of fever therapy and so forth.

The second influence which has unquestionably given the venereal disease control movement the prestige it has so long lacked is the outspoken expressions and policy of the Surgeon General of the United States Public Health Service, Dr. Thomas Parran, Jr. Challenged at the start by the refusal of one of the national broadcasting companies to permit him to discuss the subject of syphilis over the air, his persistent efforts [30a,c,d] in the matter have enlisted the interest and coöperation of even the most lethargic members of the profession, the press and the public.

The third potent influence for the successful future of the syphilis control program is the provision of the sinews of war in the form of funds under the terms of the Social Security Act, allocated to the United States Public Health Service, and by them distributed on a dollar for dollar basis to the state health authorities of the country. No such provision has been available since the war emergency legislation of 1917.

A general outline of the American program can be obtained from the report of the Advisory Committee to the Surgeon General, published by the United States Public Health Service in January, 1936.[48] This program provides that the State, municipality or health district which plans to open a compaign against venereal diseases should inte-

* Syphilis clinics of the Mayo Clinic, Western Reserve University, Johns Hopkins University, University of Pennsylvania, and University of Michigan.

grate this work with the communicable disease division of its health department, but give it the separate direction and high individual autonomy implied by a full-time venereal disease control officer. A local advisory committee to the Health Department, coördinating the interests of the venereal disease division, the medical and allied professions and all voluntary agencies, is to be established in each of these jurisdictions. An adequately organized program and proportionate assistance determined by the State's venereal disease morbidity rate are provided for. Adequate treatment facilities in urban communities are to provide (1) for the diagnosis and emergency treatment of any patient who applies, or (2) of any patient who is referred by a private physician either for continued treatment or for consultative advice and opinion; and (3) finally, for any patient who is unable to afford private medical care. The establishment of clinic facilities is to be made a matter of conference among the various instrumentalities concerned, including medical school, local hospital, research and philanthropic societies with the local organized medical profession and the state and national Public Health Service. Polyclinics are preferred to isolated clinics and the support of subsidized hospitals and health centers is made contingent on their coöperation in the state program. The admission of patients to beds when required for the treatment of syphilis and gonorrhea is made a condition of continued support. Provision is made for the development of a record system for transients and transferred patients; in communities with inadequate treatment facilities surveys are provided for, followed by a conference of all concerned and a full discussion of the questions of enlisting the coöperation of local practitioners, organizing branch clinics, new clinics, publicity and so forth. The need for abolition of quack remedies and drugstore prescribing is emphasized. In rural communities, emphasis is laid on the subventionary assistance of properly qualified local physicians, the services of specially trained county health officers, special provision for transportation of patients to centers, and the development of large special treatment centers in areas such as the deep South where many negro patients are concentrated. Traveling health units are also suggested. It is stated that the free distribution of antisyphilitic drugs by the State to all sources of treatment is rational and proper, and it is advised that two arsenicals and one bismuth preparation be the minimum made available in such a program. The development of a venereal disease diagnostic and treatment center of high rank in each state is strongly urged to serve as a consultation agency for patients, the profession, and clinic throughout the State. It is impossible here to go into details of planning and organization of clinics which must be read by interested persons in the original. The follow-up and contact-tracing personnel is specified as requiring special training and full-time service.

The standard treatment systems outlined by the Coöperative Clinical Group are recommended as standard for municipal, state and national procedure insofar as the subject is thus far covered. Serologic testing of every pregnant woman is specifically urged early in the course of her pregnancy as the first rational step in the control of prenatal syphilis.[30b, 39e]

For the first time in its history the venereal disease control movement gives full cognizance to the great importance of epidemiologic work in

the control of the disease. First sharply pointed by some pungent remarks of Munson,[26] this aspect of syphilologic work developed rapidly under the pioneer observations of Dudley Smith and W. A. Brumfield at the University of Virginia.[4, 37, 38] These authors have shown with a vividness hardly surpassed by any aspect of syphilis control work in recent years both the process by which syphilis disseminates itself throughout a community and the type of detective work which is necessary in ferreting it out and bringing it under treatment control. Coincidentally, follow-up, long a species of stepchild in the majority of syphilis clinics, has received new and more serious recognition.[13, 18, 21, 25, 27a, 33, 35] Both these fields are now conceded to require careful special training for those who devote themselves to them.[48]

In the matter of laboratory facilities, the Advisory Committee has unhesitatingly urged the standardization by the State of all sero-diagnostic procedure, with the maintenance of a careful check even to the point of licensing of private laboratories performing this work. Studies of a large number of laboratories throughout the country conducted as the so-called First Serologic Conference by the United States Public Health Service, have shown astonishing discrepancies in the work of various laboratories within a State, and the various State laboratories themselves.[11, 32] It is very apparent that this subject must early engage the full attention of central and state agencies if anything like the necessary reliability and availability of our most important uncovering device, the blood test, is to be utilized. The practice of Great Britain which exercises a systematic central control of all its official stations throughout the British Isles can provide something of a model for practice in this country. The recommendations[31] of the Committee on Evaluation of Sero-diagnostic Tests for Syphilis, headed by the Surgeon General of the United States Public Health Service, begins with insistence that adequate training is necessary for all employees and that Social Security Act funds may be appropriated to bring the personnel up to an adequate standard. A system of periodic inspection of State laboratories by thoroughly trained serologists with the United States Public Health Service is to be inaugurated and made available at the request of state health officers, and comparative examinations of serologic test performance in syphilis are to be made annually. The venereal disease research laboratory of the United States Public Health Service at Stapleton, Staten Island, New York, is drawn into this work. Municipal, private and hospital laboratories are to have a comparative annual examination through the action and support of the State Laboratory organization. In return for this coöperation it is recommended that local laboratory facilities and properly qualified and subsidized local laboratories be utilized to the full in the control of syphilis.

Among the specific items on serologic test performance it is recommended that standards for the handling and drawing of blood specimens be promulgated by the Public Health Service;[48] that the technique of the originators of tests should be strictly followed by all laboratories and modifications allowed only with the approval of the central state laboratories; that laboratories be required to use the terms "positive," "negative," and "indeterminate-repeat" (doubtful) in reporting the results of sero-diagnostic tests; and that it should be made clear that

while a single test may be used by a laboratory as a first line diagnostic procedure, the adequate serologic investigation of a doubtful or indeterminate result requires not only repetition of the original test but also the simultaneous use of another test of a different type. In the field of darkfield examination, States are advised to establish laboratory coöperation for direct darkfield examination and to provide mailing kits for practitioners, with suitable publicity relative to their availability and use for the indirect darkfield examination. The examination of the spinal fluid performed at some time during the second 6 months of treatment in early syphilis and as near the start as possible in late syphilis is made a standard procedure.

The anxiety which besets some physicians lest venereal disease control be removed from the field of private practice and taken over completely by the State should be to some extent relieved by the positive assertions of policy with reference to the coöperation of private physicians. The State function is specifically outlined as consisting of (*a*) the provision of free diagnostic service of high grade, (*b*) the free distribution of antisyphilitic drugs to private physicians for use in the treatment of private patients who are or may become a danger to public health, and (*c*) the provision of consultation services, including roentgenologic and other expensive laboratory examinations for indigent patients or those normally unable to pay for expensive service. The State health organization is expected to provide the physician with modern information on the control of the disease and to encourage him in every way to prepare himself to meet the public's and the health authority's demand for an adequate standard of treatment.

In the matter of morbidity and mortality reports, the American program provides for the reporting of all cases by a numerical system including the place of residence, but not the name of the patient (*cf.* Ramsey[34]). Laboratory reports are not to be accepted as case reports. An exceedingly important feature of the modern venereal disease program is the informative and educational program for physicians. There can be no escaping the conviction after a study of this problem that the most serious difficulty confronted by a venereal disease program in a country such as the United States, where a large proportion of patients with gonorrhea or syphilis receive treatment at the hands of private physicians is that of raising the physicians' standard of knowledge and technique to that of the modern clinic, or above it. Reference has already been made to the inadequate teaching of medical students in syphilology and ways and means of improving it are considered by the Advisory Committee.[51]

In a discussion of these problems by Stokes,[39c,d] it was suggested that energy be concentrated on the physician as early in his career as possible; that in view of the demonstrable inadequacies of simon-pure oral and written didactic methods, an effort be made to concentrate on the visual, on the individual case example, and on the actual performance of technical procedure and the giving of instruction upon the patient in small groups.

Incorporation of more searching questions regarding venereal disease practice in the State Licensing Board examinations is advocated in the Public Health Department recommendations. Physicians having a special interest in venereal disease problems from their hospital intern-

ship onward, are to be made objects of special interest and solicitude by the health authorities; and on letting their interest be known they will be given every possible encouragement to learn the field and work in it. Subsidies to medical schools and teaching hospitals are recommended and a system of postgraduate instruction for practicing physicians, utilizing state, federal and academic instructional centers awaits development. Consultative service by telephone, telegraph and correspondence on a regional basis is proposed as part of State service to the practicing physician. The dissemination of informative material, including the monthly journal of the Division of Venereal Diseases of the United States Public Health Service—"Venereal Disease Information"— is emphasized.

In a public health movement of this sort, the possibility of educating the public and thus the potentially infected patient to the point where he may insist upon and, indeed, actually solicit proper antisyphilitic therapy, should engage the thorough study of any civilian public health informative program.[39a] The "backfire" educational influence on the profession of an informed public, including many societies with collateral interests such as antituberculosis organizations, public health nursing, penalogic and child hygiene organizations, health councils, social agencies, parent-teacher and women's clubs is recognized and should be fostered as a means of raising medical treatment standards of practice through the influence of the informed patient. The minimum essential knowledge for the student and physician for meeting these demands could be offered by clinic and teaching hospital organizations as brush-up courses and adapted to the now neglected instruction of interns on a basis of 56 hours of syphilogic instruction, which, under pressure, might even be reduced to 40 for small groups that can be brought into close contact with the patients and equipment. Such courses can easily be given in large cities with teaching and medical centers.[39c]

In response to the general appreciation among authorities of the great importance of special training for a venereal disease control personnel, it may be stated that a special course has been developed at Johns Hopkins University School of Public Health for the training of public health officers and at the University of Pennsylvania for the training of epidemiologic and follow-up personnel and intensive training of physicians interested in syphilis control work and devoting a portion of their time to this problem.

The fourth influence in the syphilis control campaign is the new publicity especially as reflected in the press. From a condition of affairs in which the very word was never printed, syphilis has become as DeKruif says, a "cozy household word." From the opening of the flood gates by such influential newspapers as the Chicago Tribune, has come literally a torrent of publicity. Whole front page feature articles in Sunday supplements; extended rotograve illustrations of experimental and clinical practice and technique; and the sponsoring by press and health authority of such municipal enterprises as a blood test campaign to cover every citizen of the United States' second largest city, have been expressions of this almost fevered activity. Magazines of national circulation have published the utterances of the Surgeon General, and the technique of treatment of early syphilis has been so published that

he who runs may read. Five popular books are now available where one formerly languished in obscurity. It is difficult to believe that such activity can last. Its value is yet to be determined, but is certainly considerable if not carried *ad nauseam* to self-defeat.

It will thus be seen that the program outlined for the syphilis control movement in the United States embodies practically every essential which theory and previous world practice has indicated as significant. Several lessons have already been learned. The press publicity has already markedly increased the number of persons applying for examination and treatment. Such cities as New York have greatly extended their diagnostic service through the establishment of local stations where examination for darkfield diagnosis especially, can be rapidly and effectively done. It has become very clear that laboratories must be quickly brought up to a very much higher standard of practice than has prevailed heretofore, if there is not to be an enormous crop of falsely diagnosed syphilis to encumber and shed disrepute on the program at large. Studies of the very important problems of contact-tracing and follow-up have indicated that the superiority of the voluntary approach over compulsion or enforcement tactics can be stated in percentage as summarized by the Ingrahams.[17, 19] This work indicates that the employment of a confidential persuasive approach to elicit a voluntary response from the patient, in the hands of a trained individual, is about half again as productive of usable epidemiological information as is the untrained coercive approach. The voluntary response method is likewise superior to compulsory methods in persuading the average suspected contact to submit to medical examination, and in about the same magnitude.

It is further strongly suggested by a study of persuasive *versus* compulsory methods in four large city clinics, conducted by Norman R. Ingraham, Jr., that voluntary approach is at its highest effectiveness in contact-tracing, but that an element of compulsion is a necessary and valuable part of the procedure of follow-up. Generally speaking, however, the demonstration of the relative superiority of voluntary approach in this field is an interesting confirmation of the point of view long maintained against opposition by the heads of the British venereal disease service.

There seems every probability that large-scale social organization of many types will be drawn in one way or another into the venereal disease control campaign. Conspicuously interesting, therefore, is the report of G. H. Gehrmann,[14] Medical Director of E. I. duPont de Nemours and Company, on the problems which have been encountered on the effort of this great industrial organization to modernize its reactions and methods in the light of present-day knowledge of syphilis. It is notable that no difficulty was encountered in examining new employees, and that less than 10% of old employees refused the blood serologic test for syphilis. In all, 36,794 employees have been examined, and 1488 (4%) found to be infected. The organization operates its own laboratory on modern standards. The results of blood tests, whether positive or negative, are kept confidential between the employee and the medical division except in the case of a person who refuses to take adequate treatment, in which case the department head is advised and the employee discharged. Persons suffering with syphilis are not

excluded from employment nor are employees in the organization discharged on this account, but continued employment is contingent upon the employee's willingness to take treatment. There are, however, four exceptions to this rule: (1) food handlers, (2) employees engaged in the handling of any materials which are used in foods or for the wrapping of foods, (3) employees exposed to lead compounds, (4) employees with evidence of neurosyphilis. It is surprising, interesting and regrettable that with so modern an approach to the problem on the part of an industrial organization, the inadequacy of knowledge and non-coöperativeness of physicians at large have brought the scheme to the point where its industrial sponsors consider the situation unsatisfactory. Gehrmann summarizes with comment that demands exact quotation, for it is a genuinely tragic reflex of a situation probably of national extent, which more than any other single item in the whole venereal disease control program threatens the hope of the future:

"Most physicians demand prices for treatment that are beyond the means of the individuals and out of reasonable proportion to their incomes. Some physicians maintain these high prices despite the fact that they are receiving arsphenamine, neoarsphenamine, and bismuth free of cost from their State.

"Many physicians refuse to treat the referred cases, stating that no treatment is indicated, in spite of 4+ Kahn and Wassermann reactions although the cases have never received adequate treatment.

"Numerous physicians refuse to admit that their patients have syphilis (again in the face of 4+ Kahn and Wassermann reactions). This group denies the validity of blood tests and states that they have known their patients for years, and further know that these same patients could not have contracted syphilis without their (the doctors') knowledge.

"On several occasions the attending physician has sent a blood specimen to a private or State laboratory and the report has come back that the reaction is negative. In every instance the results obtained by the company laboratory have been corroborated by subsequent check, but the attending physician has not always admitted that the patient has syphilis.

"Many cases are discharged as having had sufficient treatment, after three to ten injections of neoarsphenamine without a heavy metal.

"Some are being treated with pills and nothing else.

"Treatment at the free clinics is very satisfactory but it is not always possible for employees to conform to clinic hours and in some places the clinics refuse to treat any patient who is employed. The evidence presented above indicates that the incidence of syphilis in industry is of sufficient extent to be well worth consideration both from the standpoint of public health and industrial risk. The problem of getting these cases adequately treated is extremely difficult, and the question arises, is it advisable for industry to assume the entire obligation of treating these cases?

"There is no question but that this work is well worthwhile, and there is no question about the adequacy of the treatment which the majority of these infected employees receive. But it does seem advisable for the industry to take over the entire management of these patients and thus insure to them continuous and proper treatment."

There can be no question in the minds of those who have followed the

venereal disease control movement for years that there exists in the United States at this time an extraordinary combination of the will to accomplishment and the means therefor. For the future to be as bright as many students believe to be possible, and all concerned hope will be the case, two elements are vitally essential. The first is an exceptional spirit of informed coöperativeness on the part of the medical profession and the second is a consistent and tactful regard for human nature as the great determining influence in conduct—for this, after all, underlies all problems of health.

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